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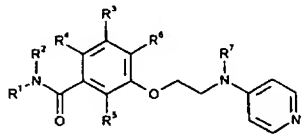
(54) Title: BENZAMIDE DERIVATIVES AS THROMBIN INHIBITORS

(57) Abstract



(I)

The invention relates to a novel class of amide derivatives which act as thrombin inhibitors as described by formula (I), where R^1 and R^2, independently represent a group (a) or R^1 and R^2 together form a C_{3-7} heterocycloalkyl or heterocycloalkenyl group which may be optionally substituted by C_{1-6} alkyl, C_{1-4} alkoxy, halogen, carboxylic acid or a C_{1-4} carboxylic acid ester group; R^3 represents hydrogen, C_{1-3} alkyl, halogen, or C_{1-2} alkoxy; R^4, R^5 and R^6 independently represent hydrogen, or halogen; R^7 represents hydrogen or C_{1-6} alkyl; R^8 represents hydrogen, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkenyl, aryl or heteroaryl, which groups are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17}; X represents a bond, a C_{1-6} alkyl chain, or a C_{2-6} alkenyl chain, where one or two nitrogen, oxygen, or sulfur atoms may be optionally contained within each chain, and the chains are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17}; R^9-R^{17} represent hydrogen, C_{1-6} alkyl, or R^9 and R^{10} or R^{15} and R^{16} form a C_{3-7} heterocycloalkyl ring, or R^{12} additionally may represent trifluoromethyl; and pharmaceutically acceptable derivatives or solvates thereof, to processes for their preparation; and their use in the treatment of clinical conditions susceptible to amelioration by administration of a thrombin inhibitor.

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BENZAMIDE DERIVATIVES AS THROMBIN INHIBITORS

This invention relates to a new class of chemical compounds and to their use in medicine. In particular, the invention concerns novel amide derivatives, methods for their preparation, pharmaceutical compositions containing them and their use as thrombin inhibitors. Thrombin inhibitors have been described previously in, for example, WO94/20467.

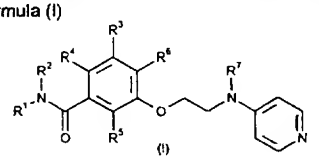
Thrombin is a serine proteinase present in plasma and is formed by conversion from its prothrombin precursor by the action of Factor Xa. Thrombin plays a central role in the mechanism of blood coagulation by converting the soluble plasma protein, fibrinogen, into insoluble fibrin. The insoluble fibrin matrix is required for the stabilisation of the primary hemostatic plug. Many significant disease states are related to abnormal hemostasis. With respect to the coronary arterial vasculature, abnormal thrombus formation due to the rupture of an established atherosclerotic plaque is the major cause of acute myocardial infarction and unstable angina. Both treatment of an occlusive coronary thrombus by thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA) are often accompanied by an acute thrombotic reclosure of the affected vessel which requires immediate resolution. With respect to the venous vasculature, a high percentage of patients undergoing major surgery in the lower extremities or the abdominal area suffer from thrombus formation in the venous vasculature which can result in reduced blood flow to the affected extremity and a pre-disposition to pulmonary embolism. Disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer and is characterised by the rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the vasculature leading to widespread organ failure.

Beyond its direct role in the formation of fibrin rich blood clots, thrombin has been reported to have profound bioregulatory effects on a number of cellular components within the vasculature and blood, (Shuman, M.A., Ann. NY Acad. Sci., 405: 349 (1986)).

The inhibition of thrombin has been implicated as a potential treatment for a number of disease states. Thrombin inhibitors may be useful in the treatment of acute

vascular diseases such as coronary thrombosis, stroke, pulmonary embolism, deep vein thrombosis, restenosis, atrial fibrillation, myocardial infarction, and unstable angina. They have been described as anti-coagulant agents both in-vivo and ex-vivo, and in oedema and inflammation, whereby a low dose of thrombin inhibitor can reduce platelet and endothelial cell thrombin mediated inflammatory responses without concomitant anticoagulant effects. Thrombin has been reported to contribute to lung fibroblast proliferation, thus, thrombin inhibitors could be useful for the treatment of some pulmonary fibrotic diseases. Thrombin inhibitors have also been reported in the treatment of tumour metastasis whereby the thrombin inhibitor prevents the fibrin deposition and metastasis caused by the inappropriate activation of Factor X by cysteine proteinases produced by certain tumour cells. They have been shown to inhibit neurite retraction and thus may have potential in neurogenerative diseases such as Parkinson's and Alzheimer's disease. They have also been reported to be used in conjunction with thrombolytic agents by permitting the use of a lower dose of thrombolytic agent. Other potential uses have been described in US5371091 for the treatment of Kasabach Merritt Syndrome and hemolytic uremic syndrome, in EP565897 for the prevention of fibrin deposits in the eye during ophthalmic surgery, and in DE4126277 for the treatment of osteoporosis.

Thus, we have now found a novel class of amide derivatives which act as thrombin inhibitors shown as formula (I)



(I)

where

R^1 and R^2 independently represent a group

or R^1 and R^2 together form a C_{3-7} heterocycloalkyl or heterocycloalkenyl group which may be optionally substituted by C_{1-6} alkyl, C_{1-4} alkoxy, halogen, carboxylic acid or a C_{1-4} carboxylic acid ester group;

R^3 represents hydrogen, C_{1-3} alkyl, halogen, or C_{1-2} alkoxy;

R^4, R^5 and R^6 independently represent hydrogen, or halogen;

R^7 represents hydrogen or C_{1-6} alkyl;

R^8 represents hydrogen, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkenyl, aryl, or heteroaryl, which groups are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17};

X represents a bond, a C_{1-6} alkyl chain, or a C_{3-6} alkenyl chain, where one or two nitrogen, oxygen, or sulfur atoms may be optionally contained within each chain, and the chains are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17};

R^9-R^{17} represent hydrogen, C_{1-6} alkyl, or R^9 and R^{10} or R^{15} and R^{16} form a C_{3-7} heterocycloalkyl ring, or R^{12} additionally may represent trifluoromethyl;

and pharmaceutically acceptable derivatives or solvates thereof.

Referring to the general formula (I), alkyl includes both straight and branched chain saturated hydrocarbon groups.

Referring to the general formula (I), alkenyl includes both straight and branched chain hydrocarbon groups with at least one double bond.

Referring to the general formula (I), aryl includes optionally substituted monocyclic or bicyclic aromatic carbocyclic groups such as phenyl and naphthyl.

Referring to the general formula (I), heteroaryl includes 5 or 6 membered aromatic heterocyclic rings containing one or more heteroatoms selected from nitrogen, sulphur and oxygen atoms, and fused bicyclic ring systems containing one or more nitrogen, sulfur, and oxygen atoms. Examples of such groups include oxadiazole, thiazole, thiadiazole, triazole, tetrazole, benzimidazole, pyridine, furan and thiophene.

Referring to the general formula (I), examples of C_{3-7} cycloalkyl groups include cyclohexyl and cyclopentyl groups.

Referring to the general formula (I), a C_{3-7} cycloalkenyl group includes rings containing at least one double bond incorporated in the ring.

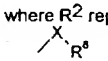
Referring to the general formula (I), a C_{3-7} heterocycloalkyl group includes rings containing containing one or more heteroatoms selected from nitrogen, sulphur and oxygen atoms, for example, a tetrahydropyran-4-yl group.

Referring to the general formula (I), a C_{3-7} heterocycloalkenyl group includes rings containing one or more heteroatoms selected from nitrogen, sulphur and oxygen atoms, together with at least on double bond incorporated in the ring.

Referring to the general formula (I) where R^1 represents a group

X is suitably a bond or C_{1-6} alkyl group, e.g. methyl, isopropyl or isobutyl, and R^8 suitably represents hydrogen, C_{3-7} cycloalkyl, aryl, or heteroaryl. When X represents a bond, R^8 is preferably phenyl optionally substuituted by one or more halogen groups, or C_{3-7} cycloalkyl, e.g. cyclobutyl, cyclopentyl or cyclohexyl. When X represents a C_{1-6} alkyl group, R^8 is preferably hydrogen, cycloalkyl, e.g. cyclohexyl, or heteroaryl, e.g. thienyl or furyl.

Referring to the general formula (I) where R^2 represents a group



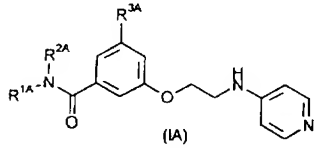
X is suitably C_{3-6} alkenyl, e.g. allyl, or C_{1-6} alkyl, e.g. methyl, ethyl, propyl or pentyl, which optionally contains an oxygen group within the chain and is optionally substituted by a group selected from hydroxy, C_{1-6} alkoxy, NHSO2R^{12}, CO_2R^{14}, $CONR^{15}R^{16}$, or SO_2NHR^{17}, and R^8 is suitably hydrogen, C_{3-7} heterocycloalkyl, e.g. pyrrolidine or morpholine, aryl, e.g. phenyl which is optionally substituted by CO_2R^{14}, or heteroaryl, e.g. oxadiazole optionally substituted by hydroxy, triazole, or tetrazole optionally substituted by C_{1-6} alkyl.

R^3 is preferably C_{1-3} alkyl, e.g. methyl, or halogen, e.g. chlorine or bromine.

R^4, R^5 and R^6 are preferably hydrogen, or halogen, e.g. fluorine.

R^7 is preferably hydrogen.

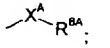
A preferred subclass of the compounds of formula (I) is defined by compounds of formula (IA)



(IA)

where

R^{1A} represents a group



X^A represents a bond or C_{1-6} alkyl;

R^{8A} represents hydrogen, C_{3-7} cycloalkyl, aryl optionally substituted by halogen, or heteroaryl;

R^{2A} represents a group

X^B represents C_{1-6} alkyl optionally substituted by CO_2R14A

R^{8B} represents hydrogen, phenyl substituted by CO_2R^{14A}, oxadiazole substituted by a hydroxy group, or an unsubstituted C-linked tetrazole group;

R^{3A} represents C_{1-3} alkyl or halogen;

and pharmaceutically acceptable derivatives or solvates thereof.

Suitable compounds of general formula (I) for use according to the invention are:

N-Cyclohexyl-3,N-dimethyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

3-Chloro-N-cyclohexyl-N-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

3-Bromo-N-cyclohexyl-N-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

N-Allyl-3-chloro-N-cyclohexyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

N-Allyl-3-bromo-N-cyclohexyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclohexyl-amino)-acetic acid;

({3-Bromo-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclohexyl-amino)-acetic acid;

N-Allyl-3-chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

N-Allyl-3-bromo-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

3-Chloro-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(tetrahydro-pyran-4-yl)-benzamide;

3-Bromo-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(tetrahydro-pyran-4-yl)-benzamide;

3-Chloro-N-propyl-N-pyridin-3-yl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

3-Bromo-N-propyl-N-pyridin-3-yl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

3-Chloro-N-(3,5-difluorophenyl)-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

3-Bromo-N-(3,5-difluorophenyl)-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

2-{{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2,4-difluoro-benzyl)-amino}-butyric acid;

4-[({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-methyl]-benzoic acid;

4-[2-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-ethyl]-benzoic acid;

3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-trifluoromethanesulfonylamino-propyl)-benzamide;

3-Chloro-N-isopropyl-N-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

N-[2-(3-Amino-[1,2,4]oxadiazol-5-yl)-ethyl]-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

N-(2-Carbamoyl-ethyl)-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

N-(2-Carbamoyl-ethyl)-3-chloro-N-cyclopropylmethyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

N-(2-Carbamoyl-ethyl)-3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(tetrahydro-furan-2-ylmethyl)-benzamide;

N-(2-Carbamoyl-ethyl)-3-chloro-N-(2,2-dimethyl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

N-(2-Carbamoyl-ethyl)-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

N-(2-Carbamoyl-ethyl)-3-chloro-N-isobutyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

6-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-benzyl)-amino]-

hexanoic acid;
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-hexanoic acid;
6-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-methoxy-ethyl)-amino]-hexanoic acid;
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclohexylmethyl-amino)-hexanoic acid;
6-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(3-fluoro-benzyl)-amino]-hexanoic acid;
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-pyridin-4-ylmethyl-amino)-hexanoic acid;
N-(5-Carbamoyl-pentyl)-3-chloro-N-furan-2-ylmethyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(5-Carbamoyl-pentyl)-3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2,2,2-trifluoro-ethyl)-benzamide;
N-(5-Carbamoyl-pentyl)-3-chloro-N-(2-fluoro-benzyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(5-Carbamoyl-pentyl)-3-chloro-N-(2-methoxy-ethyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(5-Carbamoyl-pentyl)-3-chloro-N-cyclohexylmethyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(5-Carbamoyl-pentyl)-3-chloro-N-isobutyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(5-Carbamoyl-pentyl)-3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-N-thiophen-2-ylmethyl-benzamide;
1-{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-piperidine-2-carboxylic acid;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclobutyl-amino)-butyric acid;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-furan-2-ylmethyl-amino)-butyric acid;
4-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(3-fluoro-benzyl)-amino]-butyric acid;
{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-(2-methyl-piperidin-1-yl)-methanone;
3-Chloro-N-(2-diethylcarbamoyl-ethyl)-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

3-Chloro-N-isopropyl-N-(3-methanesulfonylamino-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-[3-(propane-1-sulfonylamino)-propyl]-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-(3-oxo-3-piperidin-1-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-[2-(ethyl-methyl-carbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-(3-oxo-3-pyrrolidin-1-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-(3-morpholin-4-yl-3-oxo-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide mixture with 3-({3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isopropyl-amino)-propionic acid (1:2);
N-(2-tert-Butylcarbamoyl-ethyl)-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-[2-(2,2-dimethyl-propylcarbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-(3-oxo-3-thiomorpholin-4-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-(3-oxo-3-thiazolidin-3-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-(3-ethanesulfonylamino-propyl)-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-[3-(propane-2-sulfonylamino)-propyl]-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-(4-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-[1,2,4]triazol-1-yl-propyl)-benzamide;
3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-[1,2,4]triazol-1-yl-ethyl)-benzamide;
3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(4-[1,2,4]triazol-1-yl-butyl)-benzamide;
3-Chloro-N-(4-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-tetrazol-2-yl-propyl)-benzamide;
3-Chloro-N-(3-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-tetrazol-2-yl-propyl)-benzamide;
3-Chloro-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-tetrazol-2-yl-

propyl)-benzamide;
3-Chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-tetrazol-2-yl-ethyl)-benzamide;
3-Chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-[1,2,3]triazol-2-yl-ethyl)-benzamide;
3-Chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[2-(pyridin-2-yloxy)-ethyl]-benzamide;
3-Chloro-N-isopropyl-N-(2-methoxy-ethyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-thiophen-2-ylmethyl-amino)-hexanoic acid;
6-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-methyl-butyl)-amino]-hexanoic acid;
{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-(2,5-dimethyl-pyrrolidin-1-yl)-methanone;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-naphthalen-1-ylmethyl-amino)-butyric acid;
4-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(1-methyl-1H-benzoimidazol-2-yl)-amino]-butyric acid;
3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-trifluoromethanesulfonylamino-propyl)-benzamide;
N-(3-Amino-propyl)-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclopentyl-amino)-acetic acid;
3-Chloro-N-cyclopentyl-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-cyclopentyl-N-(3-hydroxy-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(tetrahydro-pyran-4-yl)-benzamide;
3-Chloro-N-cyclopentyl-N-(2,3-dihydroxy-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-cyclopentyl-N-(3-morpholin-4-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclopentyl-amino)-butyric acid ethyl ester;

3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-pyrrolidin-1-yl-propyl)-benzamide;
N-(3-Carbamoyl-propyl)-3-chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-Carbamoylmethyl-3-chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-ethyl-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-cyclopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N,N-dipropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclopentyl-amino)-butyric acid;
N-(2-Carbamoyl-ethyl)-3-chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-(2-chloro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
4-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-phenyl)-amino]-butyric acid methyl ester;
4-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-phenyl)-amino]-butyric acid;
3-Chloro-N-(2-fluoro-phenyl)-N-(4-oxo-4-pyrrolidin-1-yl-butyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(3-Carbamoyl-propyl)-3-chloro-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
4-({2-Carbamoyl-phenyl}-{3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-amino)-butyric acid methyl ester;
4-({2-Carbamoyl-phenyl}-{3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-amino)-butyric acid;
3-Chloro-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[3-(1H-tetrazol-5-yl)-propyl]-benzamide;
3-Chloro-N-[2-(2,3-dihydroxy-propoxy)-ethyl]-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

(R)-1-{3-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-phenyl)-amino]-propyl}-pyrrolidine-2-carboxylic acid;
3-Chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-sulfamoyl-ethyl)-benzamide;
3-Chloro-N-[2-(ethyl-methyl-carbamoyl)-ethyl]-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-[2-(ethyl-methyl-carbamoyl)-ethyl]-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-tert-Butylcarbamoyl-ethyl)-3-chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-[2-(2,2-dimethyl-propylcarbamoyl)-ethyl]-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-(3-oxo-3-thiomorpholin-4-yl-propyl)-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-(3-oxo-3-thiazolidin-3-yl-propyl)-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

3-Chloro-N-isopropyl-N-[2-(1-methyl-1H-tetrazol-5-yl)-ethyl]-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-(3,5-difluoro-phenyl)-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-(3-morpholin-4-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(tetrahydro-pyran-4-yl)-benzamide;
3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-pyrrolidin-1-yl-propyl)-N-(tetrahydro-pyran-4-yl)-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-(1-propyl-butyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-cyclopentyl-N-(4-oxo-4-pyrrolidin-1-yl-butyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-ethyl-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[1,3,4]thiadiazol-2-yl-benzamide;
3-Chloro-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-thiazol-2-yl-benzamide;
3-Chloro-N-[2-(2,3-dihydroxy-propoxy)-ethyl]-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-tert-Butylsulfamoyl-ethyl)-3-chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-

benzamide;
3-Chloro-N-(2-isopropylsulfamoyl-ethyl)-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[2-(pyridin-2-yloxy)-ethyl]-benzamide;
3-Chloro-N-[2-(2,3-dihydroxy-propoxy)-ethyl]-N-(4-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[2-(1H-tetrazol-5-yl)-ethyl]-benzamide;

3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-[1,2,4]triazol-1-yl-ethyl)-benzamide;

3-Chloro-N-[2-(3-methyl-but-2-yl-carbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-[2-(3,3-dimethyl-but-2-yl-carbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-[2-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-tert-Butyl-N-(2-tert-butylcarbamoyl-ethyl)-3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-tert-Butylcarbamoyl-ethyl)-3-chloro-N-cyclobutyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-cyclobutyl-N-[2-(2,2-dimethyl-propylcarbamoyl)-ethyl]-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-cyclobutyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide ;
3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-sulfamoyl-ethyl)-benzamide ;
3-Chloro-N-(2,2-dimethyl-propylsulfamoyl-ethyl)-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide ;
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isopropyl-amino)-hexanoic acid ;
N-(2-tert-Butylcarbamoyl-ethyl)-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(5-tert-Butylcarbamoyl-pentyl)-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide ;

3-Chloro-N-[5-(2,2-dimethyl-propylcarbamoyl)-pentyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide ;
N-(5-Carbamoyl-pentyl)-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide ;
3-Chloro-N-(2-(4-tert-butylphenyl)-ethyl)-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-[2-(1,1-dimethyl-propylcarbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-(3-oxo-3-thiazolidin-3-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-[2-(2,2-dimethylpropylcarbamoyl)-ethyl]-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-(Isopropyl-[3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl]-amino)-propionic acid;
3-(Isopropyl-[3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl]-amino)-propionic acid methyl ester;
N-(5-tert-Butylcarbamoyl-pentyl)-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
6-({3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isopropyl-amino)-hexanoic acid;
N-(2-Cyano-ethyl)-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N,N-diisopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)ethoxy]-N-[3-(2,2-dimethyl-propionylamino)-propyl]-benzamide;
3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)ethoxy]-N-[3-(3,3-dimethyl-butyrylamino)-propyl]-benzamide;
6-({3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isopropyl-amino)-hexanoic acid;
and pharmaceutically acceptable derivatives or solvates thereof.

Particularly suitable compounds of the invention include:
3-Chloro-N{2-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-ethyl}-N-isopropyl-5-[2[(pyridin-4-ylamino)-ethoxy]-benzamide ;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclobutyl-amino)-butyric acid;

6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-hexanoic acid;
4-[({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-methyl]-benzoic acid ;
4-[2-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-ethyl]-benzoic acid;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclopentyl-amino)-butyric acid ethyl ester;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclopentyl-amino)-butyric acid;
3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[2-(1H-tetrazol-5-yl)-ethyl]-benzamide;
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclohexylmethyl-amino)-hexanoic acid;
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]benzoyl}-thiophen-2-ylmethyl-amino)-hexanoic acid;
4-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-phenyl)-amino]-butyric acid methyl ester;
4-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-phenyl)-amino]-butyric acid;
3-Chloro-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[3-(1H-tetrazol-5-yl)-propyl]-benzamide;
and pharmaceutically acceptable derivatives or solvates thereof.

By "a pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of formula (I) or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds of formula (I).
It will be appreciated by those skilled in the art that the pharmaceutically acceptable derivatives of the compounds of formula (I) may be derivatised at more than one position.

Preferred pharmaceutically acceptable derivatives of the compounds of formula (I) are pharmaceutically acceptable salts thereof.

Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene- p-sulphonic, di-para-toluoyl tatrate, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.

The compounds of formula (I) are thrombin inhibitors and as such are useful in the treatment of clinical conditions susceptible to amelioration by administration of a thrombin inhibitor. Such conditions include: acute vascular diseases such as coronary thrombosis, stroke, pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion, restenosis, and atrial fibrillation; in oedema and PAF mediated inflammatory diseases such as adult respiratory shock syndrome and reperfusion damage; the treatment of disseminated intravascular coagulopathy as a result of e.g. septic shock; the treatment of pulmonary fibrosis; the treatment of tumour metastasis; neurogenerative disease such as Parkinson's and Alzheimer's diseases; viral infection; Kasabach Merritt Syndrome; Haemolytic uremic syndrome; arthritis; and osteoporosis. They may also be useful as anti-coagulants for extracorporeal blood in for example, dialysis, blood filtration, bypass, and blood product storage; and in the coating of invasive devices such as prostheses, artificial valves and catheters in reducing the risk of thrombus formation.

The ability of the compounds of formula (I) to inhibit thrombin may be exhibited by methods as described hereinafter.

Accordingly the present invention provides a method of treatment of a mammal, including man, suffering from conditions susceptible to amelioration by a thrombin inhibitor which method comprises administering to the subject an effective amount of

a compound of general formula (I) or a pharmaceutically acceptable derivative thereof.

References in this specification to treatment include prophylactic treatment as well as the alleviation of symptoms.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use as a therapeutic agent for use in medicine, particularly human medicine.

In a further aspect, the invention provides the use of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of a condition susceptible to amelioration by a thrombin inhibitor.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The compounds of the present invention may be used in combination with other antithrombotic drugs such as thromboxane receptor antagonists, prostacyclin mimetics, phosphodiesterase inhibitors, fibrinogen antagonists, thrombolytic drugs such as tissue plaminogen activator and streptokinase, non-steroidal anti-inflammatory drugs such as aspirin, and the like.

Thus the compounds for use according to the present invention may be formulated for oral, buccal, parenteral, topical, rectal, or transdermal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or the nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically

acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch, sodium starch glycollate or croscarmellose sodium); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. The capsules may contain a non-aqueous liquid formulation, for example, a solution or suspension. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds according to the present invention may be formulated for parenteral administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds according to the present invention may be formulated for topical administration by insufflation and inhalation. Examples of types of preparation for topical administration include sprays and aerosols for use in an inhaler or insufflator.

Powders for external application may be formed with the aid of any suitable powder base, for example, lactose, talc, or starch. Spray compositions may be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as metered dose inhalers, with the use of a suitable propellant.

The compounds according to the present invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

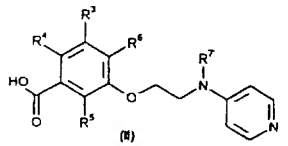
In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously, transcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds according to the present invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

As stated above, the compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

A proposed dose of the compounds according to the present invention for administration to a human (of approximately 70kg body weight) is 0.01mg to 10g, suitably 0.1mg to 1g of the active ingredient per unit dose, expressed as the weight of free base. The unit dose may be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated. The precise dose and route of administration will ultimately be at the discretion of the attendant physician or veterinarian.

The compounds of the invention may be prepared by any of the processes known in the art for the preparation of similar compounds. For example, according to a first process (A) wherein R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as previously defined, compounds of formula (I) may be prepared by reaction of a compound of formula (II) with a compound of formula (III),

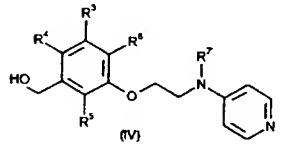


(II)

(III)

where $R^{7'}$ represents R^7 or a suitable protecting group such as tert-butoxycarbonyl. The reaction is carried out in the presence of an activating agent or agents such as 1-hydroxybenzotriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), and a base such as ethyldiisopropylamine in a suitable solvent such as N,N-dimethylformamide, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinolone in a suitable solvent such as acetonitrile, bromo-tris-pyrrolidino-phosphonic hexafluorophosphate in a suitable solvent such as N,N-dimethylformamide, or oxalyl chloride in a suitable solvent such as dichloromethane, followed by deprotection, where appropriate, of any protecting groups present under standard conditions, e.g. acidic conditions for the removal of a tert-butoxycarbonyl group.

Compounds of formula (II) may be prepared by oxidation of the corresponding alcohol of formula (IV)

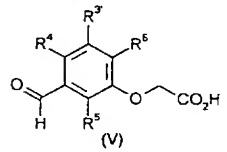


(IV)

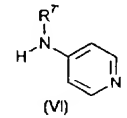
where $R^{7'}$ is as defined above. The conversion is effected by treatment of the alcohol with an oxidising agent such as manganese dioxide or dichlorodicyanobenzoquinone in a suitable solvent such as 1,4-dioxan to give the

corresponding aldehyde which is then treated with an oxidising agent such as sodium chlorite in the presence of sulfamic acid in a mixture of water and 1,4-dioxan.

Where R^3 is C_{1-3} alkyl or C_{1-2} alkoxy and $R^{7'}$ is defined above, compounds of formula (IV) may be prepared by reaction of compounds of formula (V) with compounds of formula (VI),



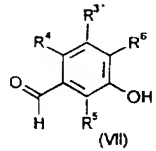
(V)



(VI)

The reaction is suitably carried out in the presence of an activating agent or agents such as TBTU in a suitable solvent such as N,N-dimethylformamide, followed by reduction of the carbonyl groups with a reducing agent such as lithium aluminium hydride in tetrahydrofuran.

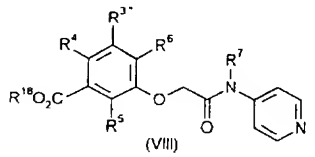
Compounds of formula (V) may be prepared from compounds of formula (VII)



(VII)

using a suitable ester of bromoacetic acid, for example ethyl, in the presence of a suitable base such as potassium carbonate in a suitable solvent such as N,N-dimethylformamide, followed by deprotection of the ester group by conventional methods, for example using a base such as aqueous sodium hydroxide in a suitable solvent such as methanol.

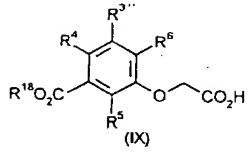
Where R^3 represents halogen and $R^{7'}$ is R^7, compounds of formula (IV) may be prepared from compounds of formula (VIII)



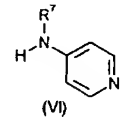
(VIII)

where $R^{3''}$ represents halogen and R^{18} represents a suitable alkyl protecting group, using a suitable reducing agent such as lithium aluminium hydride in a suitable solvent such as tetrahydrofuran.

Compounds of formula (VIII) may be prepared from compounds of formula (IX) and (VI)



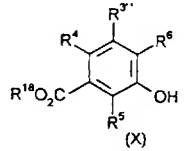
(IX)



(VI)

where $R^{3''}$ and R^{18} are previously defined. The reaction is carried out in the presence of an activating agent or agents such as 1-hydroxybenzotriazole, TBTU, and a base such as ethyldiisopropylamine in a suitable solvent such as N,N-dimethylformamide.

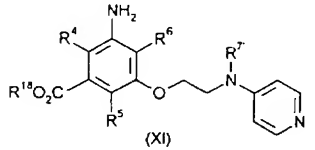
Compounds of formula (IX) may be prepared from compounds of formula (X)



(X)

where $R^{3''}$ and R^{18} are previously defined, using a suitable ester of bromoacetic acid, for example tert-butyl, in the presence of a suitable base such as potassium carbonate or sodium hydride in a suitable solvent such as N,N-dimethylformamide, followed by selective deprotection of the alkanoic ester group by conventional methods, for example cleavage under acidic conditions using trifluoroacetic acid.

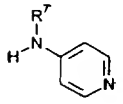
Where R^3 represents halogen, compounds of formula (II) may also be prepared from compounds of formula (XI)



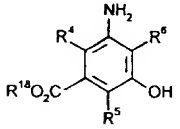
(XI)

where $R^{7'}$ is a suitable protecting group and R^{18} is as defined above, by reaction with tert-butyl nitrite and the copper (II) salt of the halide in a suitable solvent such as acetonitrile, followed by deprotection of the the ester group under suitable aqueous base conditions.

Compounds of formula (XI) may be prepared by sequential reaction of ethylene glycol di-*p*-tosylate with a compound of formula (XII) and a compound of formula (XIII)



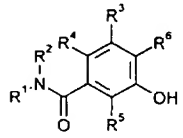
(XII)



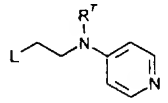
(XIII)

where $R^{7'}$ and R^{18} are as defined above, using a suitable base such as sodium hydride in a suitable solvent such as N,N-dimethylformamide.

According to a second process (B), compounds of formula (I) may be prepared by reaction of compounds of formula (XIV) and (XV)



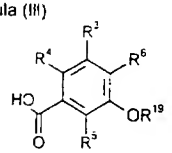
(XIV)



(XV)

where L is a suitable leaving group such as tosylate, in the presence of a suitable base such as sodium hydride in a suitable solvent such as N,N-dimethylformamide.

A compound of formula (XIV) may be prepared by reaction of a compound of formula (XVI) with a compound of formula (III)



(XVI)

where R^{19} is a suitable protecting group such as methyl, under conditions suitable for amide coupling as hereinbefore described above, followed by deprotection of R^{19} under standard conditions, for example boron tribromide removal of a methyl protecting group.

It will be appreciated that a compound of formula (X) may be reacted with a compound of formula (XV) to give a compound which can be converted to a compound of formula (I) by the methods described above and herein below.

According to a third process (C), compounds of formula (I) may be prepared by reaction of compounds of formula (II) with compounds of formula (III) which are bound to a solid phase resin via a carboxamide or carboxylate functional group on R^5 or X, by amide coupling techniques as described herein above, followed by deprotection of any protecting groups and cleavage from the resin under suitable conditions, such as acid treatment with a mixture of trifluoroacetic acid and dichloromethane. Suitable resin materials are described hereinafter with reference to the accompanying examples.

Compounds of formulae (III), (VI), (VII), (X), (XII) (XIII), (XV), and (XVI) are known compounds or may be prepared by standard methods.

It will be appreciated by persons skilled in the art that compounds of formula (I) may be prepared by interconversion, utilising other compounds of formula (I) which are optionally protected by standard protecting groups, as precursors. For instance compounds of formula (I) where R^1 or R^2 is R^8-X and X is substituted by a CN group, may be converted into compounds of formula (I) where X is substituted by e.g.

$CONH_2$, $NHSO_2R^{12}$ by methods well known in the art. Further, compounds of formula (I) which contain an SO_2NHR^{17} substituent may be prepared by coupling compounds of formula (II) with a compound of formula (III) containing a sulfonylfluoride group under standard coupling conditions, followed by reaction with a primary amine $R^{17}NH_2$, optionally in the presence of a suitable solvent such as dichloromethane, followed by deprotection of any protecting groups present.

The compounds of the invention possess thrombin inhibitory activity as determined in vitro by their ability to inhibit human α-thrombin in a chromogenic assay, using N-p-tosyl-gly-pro-lys p-nitroanilide as the chromogenic substrate. All dilutions were made in a buffer consisting of: 50 mM HEPES, 150 mM NaCl, 5 mM $CaCl_2$, 0.1% PEG and at pH 7.4. Briefly, the substrate (final conc. of 100μM) was added to thrombin (final conc. of 1nM) and the reaction monitored for 10 mins at 405nm using a Biotek EL340 plate reader; the assay was performed at room temperature. To obtain IC_{50}s the data were analyzed using Kinetically® with a 4-parameter curve fitting procedure to obtain the IC_{50} value. To determine the IC_{50} at zero and 15 mins. the compounds were preincubated with thrombin for these times prior to adding the chromogenic substrate.

The invention is further illustrated by the following intermediates and examples.

Abbreviations

hplc high performance liquid chromatography
Rt Retention time
DIPEA N-Ethyldiisopropylamine
DMF N,N-Dimethylformamide
DMAP 4-Dimethylaminopyridine
TBTU 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
HOBt 1-Hydroxybenzotriazole
PyBrop® Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
HATU® O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
9-BBN 9-borobicyclo-[3.3.1]-nonane
EEDQ= 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline

Methods

Analytical hplc was carried out on a Hewlett Packard Series II 1090 Liquid Chromatograph using a Rainin Microsorb C18 column (size 4.6 x 150mm, catalog number 80-215-C5) operating at a flow rate of 1.5 ml/min. Eluents were A: 0.1% trifluoroacetic acid/water, B: 0.05% trifluoroacetic acid/acetonitrile.
Gradients:
System 1: 15-95%B in A over 15min
System 2: 0-75%B in A over 15min
System 3: Supelcosil LCABZ+Plus column (size 4.3mm x 3.3cm; 3mm particle size) operating at 1ml/min flow rate. Eluents were A: 0.1% formic acid in 0.01M aqueous ammonium acetate, B: 0.05% formic acid in acetonitrile:water (19:1 v/v) with a gradient of 0-100%B over 3.5min and then running isocratically at 100%B for 3.5min

Retention times are given for the wavelength stated.
Preparative hplc was carried out either on on a Dynamax 60A C18 column (size 41.4mm x 25cm, catalog number 83-241-C) operating at a flow rate of 45ml/min (eluents were the same as for analytical hplc) or a Supelcosil LC-ABZ column (size 21.2mm x 25cm) operating at 15ml/min (eluents were A: 0.1% trifluoroacetic acid /water, B: 0.01% trifluoroacetic acid in 95:5 acetonitrile/water) or Supelcosil LCABZ+Plus column (size 21mm x 10cm; 5mm particle size) operating at 4ml/min flow rate (eluents were A: 0.1% formic acid in water, B: 0.05% formic acid in acetonitrile with a gradient of 0-95%B over 18.65 min.) This system used a Gilson 233XL autosampler/fraction collector.
Flash chromatography was performed on Silica gel 60 (particle size 40-63μM) Merck catalogue no. 109385

The following amines were synthesized using standard methodology:
N-Propyl-4-aminotetrahydropyran; Mass spectrum: Found: M^+ 143;
Cyclopentyl-(3-morpholin-4-yl-propyl)-amine; Mass spectrum: Found: MH^+ 213;
Cyclopentyl-(3-pyrrolidin-1-yl-propyl)-amine; Mass spectrum: Found: MH^+ 197;
4-Cyclopentylamino-butyric acid ethyl ester; Mass spectrum: Found: MH^+ 200;
3-Cyclopentylamino-propionamide; Mass spectrum: Found: MH^+ 157;
2-Cyclopentylamino-acetamide; Mass spectrum: Found: MH^+ 143;
N-Propyl-2,5-difluoroaniline; Mass spectrum: Found: MH^+172;
3-(2-Fluoro-phenylamino)-propionitrile; Mass spectrum: Found: MH^+ 165;
3-(2-Chloro-phenylamino)-propionitrile; Mass spectrum: Found: MH^+ 181;

4-(2-Fluoro-phenylamino)-butyric acid methyl ester; Mass spectrum: Found: MH^+ 212;
4-(2-Carbamoyl-phenylamino)-butyric acid methyl ester; Mass spectrum: Found: MH^+ 237;
4-(2-Fluoro-phenylamino)-butyronitrile; Hplc system 1 (λ = 254nm) Rt .8.0min;
[2-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-ethyl]-phenyl-amine and toluene-4-sulfonic acid 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester; Mass spectrum: Found: MH^+ 252;
[2-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-ethyl]-(2-fluoro-phenyl)-amine; Mass spectrum: Found: MH^+ 270;
[2-(2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-ethyl]-(4-fluoro-phenyl)-amine Mass spectrum: Found: MH^+ 270;
(R)-1-[3-(2-Fluoro-phenylamino)-propyl]-pyrrolidine-2-carboxylic acid tert-butyl ester; Mass spectrum: Found: MH^+ 323;
3-Phenylamino-propionic acid methyl ester; Mass spectrum: Found: MH^+ 180;
2-Phenylamino-ethanesulfonyl fluoride; Mass spectrum: Found: MH^+ 201;
N-(3-Pyrrolidin-1-yl-propyl)-4-aminotetrahydropyran; Mass spectrum: Found: MH^+ 213;
N-(3-Morpholin-4-yl-propyl)-4-aminotetrahydropyran; Mass spectrum: Found: MH^+ 229;
N-(2-Propylbutyl)-3-amino-propionamide; Mass spectrum: Found: MH^+ 187;
N-Propyl-2-amino-thiazole ; Mass spectrum: Found: MH^+ 143;
3-Isopropylamino propionic acid methyl ester; Mass spectrum: Found: MH^+ 146;
N-Propyl-2-amino-[1,3,4]thiadiazole; Mass spectrum: Found: MH^+ 144;
2-(2-Isopropylamino-ethyl)-N-[1,2,4]-triazole; Mass spectrum: Found: MH^+ 154;
3-(2-Isopropylamino-ethyl)-5-hydroxy-[1,2,4]oxadiaxole trifluoroacetate; Mass spectrum: Found: MH^+ 172;
4-Fluorophenyl-(3-[1,2,4]triazol-1-yl-propyl)-amine; Mass spectrum: Found: MH^+ 221;
4-Fluorophenyl-(3-tetrazol-2-yl-propyl)-amine; Mass spectrum: Found: MH^+ 222;
Cyclopentyl -(2-[1,2,4]triazol-1-yl-ethyl)-amine; Mass spectrum: Found: MH^+ 181;
Cyclopentyl -(4-[1,2,4]triazol-1-yl-butyl)-amine; Mass spectrum: Found: MH^+ 209;
3-Fluorophenyl-(3-tetrazol-2-yl-propyl)-amine; Mass spectrum: Found: MH^+ 222;
2-Fluorophenyl-(3-tetrazol-2-yl-propyl)-amine; Mass spectrum: Found: MH^+ 222;
Phenyl-(3-tetrazol-2-yl-propyl)-amine; Mass spectrum: Found: MH^+ 190;
Phenyl-(3-[1,2,3]-triazol-2-yl-propyl)-amine ; Mass spectrum: Found: MH^+ 189;

Phenyl-2-(pyridin-2-yloxy)-ethylamine; Mass spectrum: Found: MH^+ 215;
Isopropyl-2-methoxy-ethylamine; Mass spectrum: Found: MH^+ 118;
N-(3-Cyclopentylamino-propyl)-C,C,C-trifluoro-methanesulfonamide formate; Mass spectrum: Found: MH^+ 275;
5-(2-Isopropylamino-ethyl)-[1,2,4]oxadiazol-3-ylamine; Mass spectrum: Found: MH^+ 171;
3-(tert-Butylamino)-propionic acid methyl ester; Mass spectrum: Found: MH^+ 160;
3-Cyclobutylamino-propionic acid methyl ester, Mass spectrum: Found: MH^+ 158;
3-(Cyclobutylamino)propionitrile, Mass spectrum: Found: MH^+ 125;
2-Isopropylamino-ethanesulfonic acid amide, Mass spectrum: Found: MH^+ 167;
2-Isopropylamino-ethanesulfonic acid (2,2-dimethyl-propyl)-amide, Mass spectrum: Found: MH^+ 237;
3-(2-Isopropylamino-ethyl)-5-hydroxy-[1,2,4]oxadiaxole trifluoroacetate, Mass spectrum: Found: MH^+ 172;
Isopropyl-2-(4-*tert*-butylphenyl)-ethylamine, Mass spectrum: Found: MH^+ 220; and
Isopropyl-2-(pyridin-2-yloxy)-ethylamine, Mass spectrum: Found: MH^+ 181.

Intermediate 1

2-(3-Formyl-5-methyl-phenoxy)-acetic acid ethyl ester

To a stirred suspension of anhydrous potassium carbonate (1.52g) in dry DMF (20ml) was added 3-hydroxy-5-methylbenzaldehyde[1] (0.5g). The mixture was stirred under an atmosphere of nitrogen for 1.5h and then ethyl bromoacetate (0.45ml) was added. The mixture was stirred for a further 18h and then evaporated to dryness under reduced pressure. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution and the combined organic phase was washed with water, saturated lithium chloride solution, and saturated sodium chloride solution. The solution was dried over magnesium sulphate and concentrated to give the title compound as an amber-coloured gum (0.79g).
Hplc system 1 (λ = 254nm) Rt 8.0min

Intermediate 2

2-(3-Formyl-5-methyl-phenoxy)-acetic acid

A stirred solution of 2-(3-formyl-5-methyl-phenoxy)-acetic acid ethyl ester (0.79g) in methanol (4ml) at 5°C was treated with a 2M sodium hydroxide solution (3.6ml). After 15min the mixture was allowed to warm to room temperature. After a further 2h

the stirred solution was again cooled to 5°C and covered with ethyl acetate and the aqueous layer was adjusted to acidic pH with 2M hydrochloric acid. The layers were separated and the aqueous phase was extracted with more ethyl acetate. The combined organic phase was washed with water and brine and dried with magnesium sulphate. Concentration gave a gummy solid which was triturated with diethyl ether giving, after drying, the title compound (0.47g) as a pale yellow solid.
Hplc system 1 (λ = 254nm) Rt 5.2min

Intermediate 3

2-(3-Formyl-5-methyl-phenoxy)-N-pyridin-4-yl-acetamide

2-(3-Formyl-5-methyl-phenoxy)-acetic acid (0.47g) and 4-aminopyridine (0.46g) were dissolved in dry DMF (10ml). The resulting solution, stirring under a nitrogen atmosphere, was treated with TBTU (0.82g). The resulting mixture was stirred for 68h and then concentrated at reduced pressure to give a yellow viscous gum. This crude material was purified by preparative hplc. The purified product was partitioned between ethyl acetate and an aqueous solution saturated with sodium bicarbonate, sodium chloride and ammonium sulphate. The organic phase was dried over magnesium sulphate and concentrated under reduced pressure giving the title compound as an off-white solid (0.40g).
Mass spectrum: Found: MH^+ 271

Intermediate 4

{3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-methanol

A suspension of 2-(3-formyl-5-methyl-phenoxy)-N-pyridin-4-yl-acetamide (0.30g) in anhydrous tetrahydrofuran (1ml), stirring under a nitrogen atmosphere, was cooled to about 1°C and treated with a 1M tetrahydrofuran solution of lithium aluminium hydride (5.47ml) over a period of 3min. After 15min the mixture was allowed to warm to room temperature. After stirring for a further 22h the mixture was cooled to about 2°C and the excess reagent was quenched with cautious dropwise addition of wet tetrahydrofuran and then water. The resulting aqueous mixture was partitioned between ethyl acetate and dilute sodium hydroxide solution saturated with sodium chloride and ammonium sulphate. The organic phase was dried with magnesium sulphate and concentrated under reduced pressure and the resulting gum was triturated with diethyl ether giving, after drying, the title compound as an off-white solid (0.13g).
Hplc system 2 (λ = 254nm) Rt 7.6min

Intermediate 5

3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzaldehyde

A suspension of {3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-methanol (0.132g) and manganese dioxide (0.370g) in 1,4-dioxan (5ml) was heated to reflux with stirring under an atmosphere of dry nitrogen for 5h. After cooling to room temperature the mixture was filtered through Harborlite® and the pad washed with 1,4-dioxan and then methanol. The combined filtrates were evaporated to dryness under reduced pressure to give an off-white solid. Trituration with diethyl ether gave, after drying, the title compound as a white powder (0.074g).
Hplc system 2 (λ = 254nm) Rt 8.9min

Intermediate 6

3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoic acid trifluoroacetate salt

A stirred solution of 3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzaldehyde (0.074g) in a 3:2 v/v mixture of 1,4-dioxan and water (7ml) was treated with sulphamic acid (0.163g) and then sodium chlorite (0.208g). After 22h the mixture was cooled to 0°C and treated with an aqueous solution of sodium bisulphite until the mixture was colourless. The pH was adjusted to about 7 by the addition of saturated sodium bicarbonate solution and the mixture concentrated to about 5ml under reduced pressure and subjected to preparative hplc. The required fraction was concentrated and dried by addition of toluene followed by concentration at reduced pressure. This yielded the title compound as a white powder (0.061g).
Hplc system 2 (λ = 254nm) Rt 8.3min

Intermediate 7

3-Bromo-5-hydroxybenzoic acid methyl ester

A solution of sodium nitrite (5.9g) in water (17ml) was added to a stirred solution of 3-amino-5-hydroxybenzoic acid methyl ester (12.2g) in a mixture of methanol (33ml) and concentrated sulphuric acid (66ml) at 0°C over 90min. The reaction mixture was stored at 0°C and added over 2 h to a stirred mixture of copper (I) bromide (32.3g) in 8% w/v aqueous hydrobromic acid (120ml) at 65°C. After the addition was complete the reaction mixture was cooled to 0°C and then filtered. The residue was washed with water, 1M hydrochloric acid and further water. The solid was extracted with diethyl ether and the residual solids removed by filtration. The filtrate was dried

with anhydrous sodium sulphate and then concentrated under reduced pressure. This yielded the title compound as a red solid (10.5g).
Hplc system 1 (λ = 254nm) Rt 7.5min

Intermediate 8

2-(5-Bromo-3-methoxycarbonyl-phenoxy)-acetic acid tert-butyl ester

To a stirred solution of 3-bromo-5-hydroxybenzoic acid methyl ester (10.2g) and tert-butyl bromoacetate (9.7ml) in anhydrous DMF was added sodium hydride (60% dispersion in mineral oil, 2.6g). After 30min water (10ml) aws added. The reaction mixture was partitioned between ethyl acetate and water. The aqueous phase was removed and the organic phase washed with further water, 1M sodium hydroxide solution and dried with brine and over sodium sulphate. Concentration under reduced pressure gave the title compound as dark yellow gum (12.8g).
Hplc system 1 (λ = 254nm) Rt 11.4min

Intermediate 9

2-(5-Bromo-3-methoxycarbonyl-phenoxy)-acetic acid

A solution of 2-(5-bromo-3-methoxycarbonyl-phenoxy)-acetic acid tert-butyl ester (12.8g) in a mixture of dichloromethane (100ml) and trifluoroacetic acid (100ml) was stored at room temperature for 2h. The solution was concentrated under reduced pressure. The residual solid was suspended in toluene and the solvent removed under reduced pressure to give the title compound as a brown solid (10.6g).
Hplc system 1 (λ = 254nm) Rt 7.3min

Intermediate 10

2-(5-Bromo-3-methoxycarbonyl-phenoxy)-N-pyridin-4-yl-acetamide

A solution of 2-(5-bromo-3-methoxycarbonyl-phenoxy)-acetic acid (10.6g), TBTU (19.3g) and HOBt (5.1g) in dry DMF (50ml) was treated with DIPEA (9.9ml). The resulting solution was stirred under a nitrogen atmosphere and was then treated with 4-aminopyridine (3.6g) after 30min. The resulting mixture was stirred for 18h and then concentrated at reduced pressure to give a yellow viscous gum which was partitioned between ethyl acetate and water. The aqueous layer was removed and the organic phase washed with further water, 1M sodium hydroxide solution, aqueous saturated ammonium chloride, water and dried with brine and over sodium sulphate. The organic phase was concentrated under reduced pressure giving the title compound as a yellow solid (6.60g).

Hplc system 1 (λ = 254nm) Rt 6.7min

Intermediate 11

{3-Bromo-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-methanol

A stirred solution of 2-(5-bromo-3-methoxycarbonyl-phenoxy)-N-pyridin-4-yl-acetamide (6.61g) in anhydrous tetrahydrofuran (200ml) was treated with a 1M diethyl ether solution of lithium aluminium hydride (56.1ml) over a period of 20min. A brown precipitate appeared and the mixture was stirred at room temperature for 6h. The reaction mixture was treated with water (2ml) 1M sodium hydroxide solution (2ml), water (6ml) and then with 2M hydrochloric acid (150ml). The reaction mixture was extracted with ethyl acetate and then basified with 2M sodium hydroxide solution. The reaction mixture was reextracted with ethyl acetate. The first organic phase was washed with saturated aqueous sodium bicarbonate and combined with the second organic phase. The combined organic phase was washed with water and dried with brine and over sodium sulphate. Concentration of the organic phase gave a gum which was found to be unsatisfactory so the gum was partitioned between ethyl acetate and 2M hydrochloric acid. The aqueous layer was separated, basified to pH 10 and extracted with ethyl acetate. The organic phase was washed with water and dried with brine and over sodium sulphate. Concentration under reduced pressure gave the title compound as an off-white solid (1.5g).

Hplc system 1 (λ = 254nm) Rt 5.4min

Intermediate 12

3-Bromo-5-[2-(pyridin-4-ylamino)-ethoxy]-benzaldehyde

A suspension of {3-bromo-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-methanol (1.4g) and manganese dioxide (3.2g) in 1,4-dioxan (50ml) was heated to reflux with stirring under an atmosphere of dry nitrogen for 8h. After cooling to room temperature the mixture was stirred at room temperature for 16h, and then filtered through Harborlite® and the pad washed with hot methanol. The combined filtrates were evaporated to dryness under reduced pressure to give the title compound as an off-white solid (1.2g).

Hplc system 1 (λ = 254nm) Rt 9.8min

Intermediate 13

3-Bromo-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoic acid trifluoroacetate salt

A stirred solution of 3-bromo-5-[2-(pyridin-4-ylamino)-ethoxy]-benzaldehyde (1.2g) in 1,4-dioxan and water (3:2 v/v, 50ml) was treated with sulphamic acid (2.5g) and then sodium chlorite (3.2g). After 3h the mixture was treated with an aqueous solution of sodium bisulphite until the mixture was colourless. The mixture was concentrated under reduced pressure and extracted with several portions of hot ethanol. The combined ethanolic solution was concentrated under reduced pressure and purified by preparative hplc. The required fraction was concentrated and dried by addition of acetonitrile followed by concentration at reduced pressure. This yielded the title compound as a white solid (0.495g).

Hplc system 1 (λ = 254nm) Rt 9.0min

Intermediate 14

3-Amino-5-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)ethoxy]-benzoic acid methyl ester

To a stirred solution of pyridin-4-yl-carbamic acid tert-butyl ester[2] (3.9g) and ethylene glycol di-*p*-tosylate (7.4g) in DMF at room temperature under a nitrogen atmosphere was added sodium hydride (60% dispersion in mineral oil, 0.88g). Stirring was continued for 7h and then 3-amino-5-hydroxybenzoic acid, methyl ester[3] (2.5g) and sodium hydride (60% dispersion in mineral oil, 0.66g) were added. The reaction mixture was stirred for 66hr and then water (10ml) added. The mixture was concentrated under reduced pressure and the residue partitioned between 2M hydrochloric acid and ethyl acetate. The aqueous phase was separated and the organic phase reextracted with 2M hydrochloric acid. The aqueous layers were combined and neutralised with sodium hydroxide pellets and then extracted with ethyl acetate. The organic phase was washed with water and then dried with brine and over sodium sulphate. Concentration under reduced pressure gave the title compound as a dark brown gum (4.2g).

Mass spectrum: Found: MH^+ 388

Intermediate 15

3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid methyl ester

To a stirred suspension of anhydrous copper(II)chloride (0.67g) in acetonitrile (20ml) at room temperature was added tert-butyl nitrite (0.7ml). The reaction mixture was heated to reflux and a solution of 3-amino-5-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)ethoxy]-benzoic acid methyl ester (1.94g) in acetonitrile (5ml)

added. The reaction was stirred at reflux for 10min, cooled to room temperature and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 2M hydrochloric acid. The organic phase was washed with water and dried with brine and over sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with dichloromethane:methanol (50:1 v/v) to give the title compound as a red gum (0.58g).

Hplc system 1 (λ = 254nm) Rt 12.6min

Intermediate 16

3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid methyl ester (0.58g) in a mixture of 1,4-dioxane (5ml) and water (5ml) was added 2M sodium hydroxide solution (0.72ml). The reaction mixture was stirred at room temperature for 20h, acidified by the addition of 2M hydrochloric acid (0.75ml) and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water, the aqueous layer removed and the organic phase washed with further water and dried with brine and over sodium sulphate. Concentration of the organic phase under reduced pressure gave the title compound as a yellow solid (0.32g).

Hplc system 1 (λ = 254nm) Rt 7.7min

Intermediate 17

{2-[3-Chloro-5-(cyclohexyl-methyl-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.039g), TBTU (0.064g) and HOBt (0.027g) in DMF (1ml) was added DIPEA (0.036ml) followed by N-methylcyclohexylamine (0.027ml) after 15min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.036g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1(λ = 254nm) Rt 10.7min

Intermediate 18

{2-[3-(Allyl-cyclopentyl-carbamoyl)-5-chloro-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.039g), TBTU (0.064g) and HOBt (0.027g) in DMF (1ml) was added DIPEA (0.036ml) followed by N-allylcyclopentylamine (0.029ml) after 15min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.030g) obtained by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 11.0min

Intermediate 19

{2-[3-(Allyl-cyclohexyl-carbamoyl)-5-chloro-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.039g), TBTU (0.064g) and HOBt (0.027g) in DMF (1ml) was added DIPEA (0.036ml) followed by N-allylcyclohexylamine (0.029ml) after 15min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.032g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 11.5min

Intemediate 20

{2-[3-(Propyl -cyclopentyl-carbamoyl)-5-chloro-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

A suspension of 5% Pd on carbon (0.01g) in a solution of {2-[3-(allyl-cyclopentyl-carbamoyl)-5-chloro-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.07g) in toluene (10ml) was stirred under an atmosphere of hydrogen for 2h. The catalyst was filtered through diatomaceous earth and the filtrate evaporated to give the title compound as a pale yellow gum (0.07g).

Mass spectrum: Found: MH^+ 502 (^{35}Cl)

Intermediate 21

{2-{3-Chloro-5-[cyclopentyl-(3-hydroxy-propyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To {2-[3-(allyl-cyclopentyl-carbamoyl)-5-chloro-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.11g) was added 9-BBN (0.5M in THF, 2.2ml) and the resulting solution stirred at room temperature under nitrogen for 20h. A mixture of 28% aqueous hydrogen peroxide solution (1.8ml) and 2M aqueous sodium hydroxide (0.9ml) was added and the reaction mixture stirred at reflux for 2h. The solvent was removed *in vacuo* and the residue purified by preparative hplc and the title compound (0.064g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Mass spectrum: Found: MH^+ 518 (^{35}Cl)

Intermediate 22

{2-{3-Chloro-5-[propyl-(tetrahydro-pyran-4-yl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.06g), TBTU (0.096g) and HOBt (0.030g) in DMF (1ml) was added DIPEA (0.052ml) followed by N-propyl-4-aminotetrahydropyran (0.033g) as a solution in DMF (1ml) after 20min. The reaction mixture was stirred at room temperature for 20h and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic phase was washed with further water and saturated aqueous sodium bicarbonate and dried with brine and over sodium sulphate and concentrated under reduced pressure to give the title compound as a gum (0.07g).

Mass spectrum: Found: MH^+ 518 (^{35}Cl)

Intermediate 23

{2-{3-Chloro-5-[cyclopentyl-(2,3-dihydroxy-propyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a solution of {2-[3-(allyl-cyclopentyl-carbamoyl)-5-chloro-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.075g) in a mixture of acetone (1.0ml) and water (0.5ml) was added osmium tetroxide (1.52 ml of a 2.5% solution in tert-butanol). After 16h excess sodium sulphite was added to the reaction mixture and the mixture partitioned between chloroform and water. The organic layer was concentrated to give the title compound (0.044g) which was used without further purification.

Intermediate 24

{2-{3-Chloro-5-[cyclopentyl-(3-morpholin-4-yl-propyl)-carbamoyl]-phenoxy)-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester trifluoroacetate

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g), TBTU (0.096g) and HOBt (0.030g) in DMF (1ml) was added DIPEA (0.052ml) followed by cyclopentyl-(3-morpholin-4-yl-propyl)-amine (0.064g) after 5min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.060g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 6.5min

Intermediate 25

{2-{3-Chloro-5-[cyclopentyl-(3-pyrrolidin-1-yl-propyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester trifluoroacetate

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g), TBTU (0.096g) and HOBt (0.030g) in DMF (1ml) was added DIPEA (0.052ml) followed by cyclopentyl-(3-pyrrolidin-1-yl-propyl)-amine (0.059g) after 15min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.080g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Mass spectrum: Found: MH^+ 571 (^{35}Cl)

Intermediate 26

4-{{3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-cyclopentyl-amino)-butyric acid ethyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.300g), TBTU (0.482g) and HOBt (0.150g) in DMF (5ml) was added DIPEA (0.260ml) followed by 4-cyclopentylamino-butyric acid ethyl ester (0.316g) after 10min. The reaction mixture was stirred at room temperature for 16h and then further 4-cyclopentylamino-butyric acid ethyl ester (0.316g) was added After 24h, the reaction mixture was concentrated under reduced pressure to give a

viscous gum which was partitioned between ethyl acetate and water. The aqueous layer was removed and the organic phase washed with further water, aqueous saturated sodium bicarbonate solution, water and dried with brine and over sodium sulphate. The organic phase was concentrated under reduced pressure to give crude product as a black gum (0.420g) which was purified by preparative hplc and the title compound (0.189g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 1 (λ = 254nm) Rt 10.9min

Intermediate 27
4-({3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-cyclopentyl-amino)-butyric acid
2M Aqueous sodium hydroxide (0.33ml) was added to a stirred solution of 4-({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-cyclopentyl-amino)-butyric acid ethyl ester (0.189g) in 1,4-dioxan (2ml). 2M aqueous hydrochloric acid (0.33ml) was added after 1h. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was removed and the organic phase was dried with brine and over sodium sulphate and then concentrated under reduced pressure to give the title compound (0.138g) as a white foam.
Mass spectrum: Found: MH^+ 546 (^{35}Cl)

Intermediate 28
{2-{3-[(3-Carbamoyl-propyl)-cyclopentyl-carbamoyl]-5-chloro-phenoxy}-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester
To a stirred solution of 4-({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-cyclopentyl-amino)-butyric acid (0.049g), TBTU (0.058g) and HOBt (0.024g) in DMF (1ml) was added DIPEA (0.031ml) followed a 0.5M solution of ammonia in 1,4-dioxane (0.36ml) after 15min. The reaction mixture was stirred at room temperature for 43h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.040g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 545 (^{35}Cl)

Intermediate 29
{2-{3-Chloro- N-cyclopentyl-N-(4-oxo-4-pyrrolidin-1-yl-butyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester
To a stirred solution of 4-({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-cyclopentyl-amino)-butyric acid (0.028g), TBTU (0.034g) and HOBt (0.008g) in DMF (0.2ml) was added DIPEA (0.024ml) followed by pyrrolidine (0.008ml) after 15min. The reaction mixture was stirred at room temperature for 43h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.025g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 599 (^{35}Cl)

Intermediate 30
{2-{3-[(2-Carbamoyl-ethyl)-cyclopentyl-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester
To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g), TBTU (0.096g) and HOBt (0.030g) in DMF (1ml) was added DIPEA (0.052ml) followed by 3-cyclopentylamino-propionamide (0.047mg) after 10min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.074g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 531 (^{35}Cl)

Intermediate 31
{2-[3-Chloro-5-(ethyl-phenyl-carbamoyl)-cyclopentyl-phenoxy]-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester
To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g), TBTU (0.096g) and HOBt (0.030g) in DMF (1ml) was added DIPEA (0.052ml) followed by 2-cyclopentylamino-acetamide (0.043g) after 10min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.064g) was obtained as a colourless gum by

concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 531 (^{35}Cl)

Intermediate 32

{2-{3-[(2-Carbamoyl-methyl)-cyclopentyl-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g), TBTU (0.096g) and HOBt (0.030g) in DMF (1ml) was added DIPEA (0.052ml) followed by 3-cyclopentylamino-acetamide (0.043g) after 15min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.057g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 517 (^{35}Cl)

Intermediate 33

{2-{3-Chloro-5-[(2-cyano-ethyl)-cyclopropyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g), TBTU (0.096g) and HOBt (0.030g) in DMF (1ml) was added DIPEA (0.052ml) followed by 3-cyclopropylpropionitrile (0.050g) after 15min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.075g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 1 (λ = 254nm) Rt 8.1min

Intermediate 34

[2-(3-Chloro-5-dipropylcarbamoyl-phenoxy)-ethyl]-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g), TBTU (0.096g) and HOBt (0.030g) in DMF (1ml) was added DIPEA (0.052ml) followed by dipropylamine (0.030mg) after 20min. The

reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.085g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 476 (^{35}Cl)

Intermediate 35

{2-[3-Chloro-5-(ethyl-phenyl-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g), TBTU (0.096g) and HOBt (0.030g) in DMF (1ml) was added DIPEA (0.052ml) followed by N-ethylaniline (0.038ml) after 15min. The reaction mixture was stirred at room temperature for 66h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.080g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 496 (^{35}Cl)

Intermediate 36

3-Chloro-N-(3,5-difluoro-phenyl)-5-methoxy-N-propyl-benzamide

2M Oxalyl chloride solution in dichloromethane (0.210ml) and DMF (0.010ml) were added to a solution of 3-chloro-5-methoxy-benzoic acid (0.373g) in anhydrous dichloromethane (20ml). The reaction was stirred at room temperature for 2h then N-propyl-2,5-difluoroaniline (0.408g), DMAP (0.010g) and DIPEA (0.973ml) were added. The reaction mixture was stirred at room temperature for 18h, diluted with ethyl acetate and then extracted repeatedly with 2M hydrochloric acid until none of the aniline remained. The organic phase was dried with brine and over sodium sulphate and evaporated under reduced pressure to give the title compound (0.279g) as a colourless gum.
Hplc system 1 (λ = 254nm) Rt 11.1min

Intermediate 37

3-Chloro-N-(3,5-difluoro-phenyl)-5-hydroxy-N-propyl-benzamide

To a stirred solution of 3-chloro-N-(3,5-difluoro-phenyl)-5-methoxy-N-propyl-benzamide (0.164g) in anhydrous dichloromethane (5ml) at -78°C was added 1M boron tribromide solution in dichloromethane (3.5ml). The reaction mixture was stirred at this temperature for 15min. The reaction was allowed to warm to room temperature, and after 3.5h the reaction was cooled to -78°C and methanol (6ml) added. The reaction was allowed to rewarm to room temperature and the solvent removed *in vacuo*. The residue was purified by flash column chromatography eluting with cyclohexane:ethyl acetate (3:1 v/v) to give the title compound as a colourless oil (0.110g).

Hplc system 1 (λ = 254nm) Rt 9.1min

Intemediate 38

Toluene-4-sulfonic acid 2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethyl ester

To a solution of pyridin-4-yl-carbamic acid tert-butyl ester[2] (14.0g) in dry DMF (200ml) was added sodium hydride (60% dispersion in mineral oil, 3.17g) and ethylene glycol tosylate (26.7g). The reaction mixture was stirred for 16h. Water (150ml) was added and the mixture extracted with ethyl acetate, washed with brine (75ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography using eluting with chloroform:methanol (49:1 v/v) to give the title compound as a brown oil (10.7g).

Mass spectrum found: MH^+ 393

Intermediate 39

{2-[3-Chloro-5-[(propyl)-(3,5-difluoro-phenyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a solution of 3-chloro-N-(3,5-difluoro-phenyl)-5-hydroxy-N-propyl-benzamide (0.050g) in DMF (0.5ml) stirred at room temperature under nitrogen was added sodium hydride (60% dispersion in oil, 0.007 g) and after 10min was added toluene-4-sulfonic acid 2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethyl ester (0.060g). The reaction was stirred for 66h, quenched with water and then concentrated *in vacuo*. and the residue subjected to preparative hplc. The title compound (0.029g) was obtained as an colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile.

Hplc system 1 (λ = 254nm) Rt 11.1min

Intermediate 40

{2-[3-Chloro-5-[(2-cyano-ethyl)-(2-fluoro-phenyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

2M Oxalyl chloride solution in dichloromethane (0.090ml) and DMF (0.001ml) were added to a suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.059g) in anhydrous dichloromethane (1ml). The reaction was stirred at room temperature for 1.5h then a solution of 3-(2-fluoro-phenylamino)-propionitrile (0.026g) in dichloromethane (1ml), DMAP (0.002g) and DIPEA (0.078ml) were added. The reaction mixture was stirred at room temperature for 66h. The reaction mixture was partitioned between ethyl acetate and 1M aqueous hydrochloric acid. The aqueous layer was removed and the organic phase washed with further 1M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution, water and dried with brine and over sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate:cyclohexane (4:1 v/v), to give the title compound as a colourless gum (0.028g).

Hplc system 1 (λ = 254nm) Rt 9.7min

Intermediate 41

{2-[3-Chloro-5-[2-chloro-phenyl)-(2-cyano-ethyl)-(carbamoyl)-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

2M Oxalyl chloride solution in dichloromethane (0.090ml) and DMF (0.001ml) were added to a suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.059g) in anhydrous dichloromethane (1ml). The reaction was stirred at room temperature for 1.5h then a solution of 3-(2-chloro-phenylamino)-propionitrile (0.029g) in dichloromethane (1ml), DMAP (0.002g) and DIPEA (0.078ml) were added. The reaction mixture was stirred at room temperature for 66h. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was removed and the organic phase washed with further 1M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution, water and dried with brine and over sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate:cyclohexane (4:1 v/v), to give the title compound as a colourless gum (0.040g).

Hplc system 1 (λ = 254nm) Rt 9.7min

Intermediate 42

4-{[3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-(2-fluoro-phenyl)-amino]-butyric acid methyl ester

2M Oxalyl chloride solution in dichloromethane (0.600ml) and DMF (0.01ml) were added to a suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.393g) in anhydrous dichloromethane (5ml). The reaction was stirred at room temperature for 1h then a solution of 4-(2-fluoro-phenylamino)-butyric acid methyl ester (0.422g) in dichloromethane (1.5ml), DMAP (0.006g) and DIPEA (0.522ml) were added. The reaction mixture was stirred at room temperature for 2h. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous layer was removed and the organic phase washed with 1M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution, water and dried with brine and over sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate:cyclohexane (4:1 v/v), to give the title compound as a colourless gum (0.287g)

Hplc system 1 (λ = 254nm) Rt 10.5min

Intermediate 43

4-{[3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-(2-fluoro-phenyl)-amino]-butyric acid

2M Aqueous sodium hydroxide (0.75ml) was added to a stirred solution of 4-({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-(2-fluoro-phenyl)-amino)-butyric acid ethyl ester (0.270g) in 1,4-dioxan (2ml). 2M aqueous hydrochloric acid (1.0ml) was added after 16h. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was removed and the organic phase was dried with brine and over sodium sulphate and then concentrated under reduced pressure to give the title compound (0.185g) as a white foam.

Hplc system 1 (λ = 254nm) Rt 8.7min

Intermediate 44

(2-{3-[(3-Carbamoyl-propyl)-(2-fluoro-phenyl)-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 4-({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-(2-fluoro-phenyl)-amino)-butyric acid (0.100g), TBTU (0.112g) and HOBt (0.047g) in DMF (2ml) was added DIPEA (0.060ml) followed by a 0.5M solution of ammonia in 1,4-dioxane (0.70ml) after 10min. The reaction mixture was stirred at room temperature for 70h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.100g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Mass spectrum: Found: MH^+ 571 (^{35}Cl)

Intermediate 45

(2-{3-Chloro-5-[(2-fluoro-phenyl)-(4-oxo-4-pyrrolidin-1-yl-butyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 4-({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-(2-fluoro-phenyl)-amino)-butyric acid (0.025g), TBTU (0.028g) and HOBt (0.012g) in DMF (1ml) was added DIPEA (0.015ml) followed by pyrrolidine (0.007ml) after 10min. The reaction mixture was stirred at room temperature for 16h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.025g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Mass spectrum: Found: MH^+ 625 (^{35}Cl)

Intermediate 46

4-{[3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-(2-carbamoyl-phenyl)-amino]-butyric acid methyl ester

2M Oxalyl chloride solution in dichloromethane (0.090ml) and DMF (0.01ml) were added to a suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g) in anhydrous dichloromethane (1ml). The reaction was stirred at room temperature for 2h then 4-(2-carbamoyl-phenylamino)-butyric acid methyl ester (0.037g), DMAP (0.002g) and DIPEA (0.078ml) were added. The reaction mixture was stirred at room temperature for 18h. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was removed and the organic phase washed with saturated aqueous sodium bicarbonate solution, water and dried with brine and over sodium sulphate and concentrated under

reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate:cyclohexane (9:1 v/v), neat ethyl acetate and dichloromethane:methanol (9:1). to give the title compound as a colourless gum (0.031g).

Hplc system 1 (λ = 254nm) Rt 7.9min

Intermediate 47

[2-[3-Chloro-5-[(3-cyano-propyl)-2-fluoro-phenyl)-carbamoyl]-phenoxy]-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

2M Oxalyl chloride solution in dichloromethane (0.300ml) and DMF (0.01ml) were added to a suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.195g) in anhydrous dichloromethane (5ml). The reaction was stirred at room temperature for 2h then 4-(2-fluoro-phenylamino)-buyronitrile (0.178g) as a solution in dichloromethane (1ml), DMAP (0.012g) and DIPEA (0.105ml) were added. The reaction mixture was stirred at room temperature for 40h. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous layer was removed and the organic phase washed with 1M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, water and dried with brine and over sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate:cyclohexane (1:1 v/v) and neat ethyl acetate, to give the title compound as a colourless gum (0.132g).

Hplc system 1 (λ = 254nm) Rt 9.2min

Intermediate 48

[2-(3-Chloro-5-{[2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-ethyl]-phenyl-carbamoyl}-phenoxy)-ethyl]-pyridin-4-yl-carbamic acid tert-butyl ester

2M Oxalyl chloride solution in dichloromethane (0.115ml) and DMF (0.005ml) were added to a suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g) in anhydrous dichloromethane (5ml). The reaction was stirred at room temperature for 1h then a mixture of [2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-ethyl]-phenyl-amine and toluene-4-sulfonic acid 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester compound (0.194g in a ratio of 2:1mol/mol), DMAP (0.005g) and DIPEA (0.080ml) were added. The reaction mixture was stirred at room temperature for 20h. The reaction mixture was diluted with further dichloromethane and extracted with saturated aqueous sodium bicarbonate. The

aqueous layer was removed and the organic phase washed with 1M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, water and dried with brine and over sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate:petroleum ether (1:1 v/v) and neat ethyl acetate, to give the title compound as a colourless gum (0.037g)

Hplc system 1 (λ = 254nm) Rt 11.1min

Intermediate 49

(2-{3-Chloro-5-[[2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-ethyl]-(2-fluoro-phenyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

2M Oxalyl chloride solution in dichloromethane (0.115ml), and DMF (0.005ml) were added to a suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g) in anhydrous dichloromethane (5ml). The reaction was stirred at room temperature for 1.5h then [2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-ethyl]-(2-fluoro-phenyl)-amine (0.121g) as a solution in dichloromethane (0.5ml), DMAP (0.005g) and DIPEA (0.080ml) were added. The reaction mixture was stirred at room temperature for 20h. The reaction mixture was diluted with further dichloromethane and extracted with saturated aqueous sodium bicarbonate. The aqueous layer was removed and the organic phase washed with water and dried with brine and over sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate:petroleum ether (1:1, 2:1 and 4:1 v/v) and neat ethyl acetate, to give the title compound as a colourless gum (0.035g)

Hplc system 1 (λ = 254nm) Rt 11.0min

Intermediate 50

(2-{3-Chloro-5-[[2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-ethyl]-(4-fluoro-phenyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

2M Oxalyl chloride solution in dichloromethane (0.115ml) and DMF (0.005ml) were added to a suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g) in anhydrous dichloromethane (5ml). The reaction was stirred at room temperature for 1.5h then [2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-ethyl]-(4-fluoro-phenyl)-amine (0.078g) as a solution in dichloromethane (0.5ml), DMAP (0.002g) and DIPEA (0.080ml) were added. The reaction mixture was stirred at room temperature for 16h. The reaction mixture was diluted with

further dichloromethane and extracted with saturated aqueous sodium bicarbonate. The aqueous layer was removed and the organic phase washed with water and dried with brine and over sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate:petroleum ether (1:1, 2:1 and 4:1 v/v), to give the title compound as a colourless gum (0.037g)

Hplc system 1 (λ = 254nm) Rt 11.2min

Intermediate 51

(R)-1-{3-[{3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-(2-fluoro-phenyl)-amino]-propyl}-pyrrolidine-2-carboxylic acid tert-butyl ester and (R)-1-[3-(2-fluoro-phenylamino)-propyl]-pyrrolidine-2-carboxylic acid tert butyl ester

2M Oxalyl chloride solution in dichloromethane (0.112ml) and DMF (0.005ml) were added to a suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g) in anhydrous dichloromethane (2.0ml). The reaction was stirred at room temperature for 1h then a mixture of (R)-1-[3-(2-fluoro-phenylamino)-propyl]-pyrrolidine-2-carboxylic acid tert-butyl ester (0.145g), DMAP (0.002g) and DIPEA (0.080ml) as a solution in dichloromethane (0.4ml) was added. The reaction mixture was stirred at room temperature for 18h and evaporated *in vacuo*. The residue was purified by preparative hplc give the title compounds as a colourless gum (0.110g) by concentration of the required fraction under reduced pressure and drying . by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm)

Rt 8.3min ((R)-1-[3-(2-fluoro-phenylamino)-propyl]-pyrrolidine-2-carboxylic acid tert butyl ester);

Rt 9.7min ((R)-1-[3-[{3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-(2-fluoro-phenyl)-amino]-propyl}-pyrrolidine-2-carboxylic acid tert-butyl ester)

Intermediate 52

3-({3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-phenyl-amino)-propionic acid methyl ester

2M Oxalyl chloride solution in dichloromethane (1.8ml), and DMF (0.05ml) were added to a suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (1.18g) in anhydrous dichloromethane (30ml). The reaction was

stirred at room temperature for 1h then 3-phenylamino-propionic acid methyl ester (0.644g), DMAP (0.036g) and DIPEA (1.04ml) were added. The reaction mixture was stirred at room temperature for 20h and partitioned between ethyl acetate and 1M aqueous hydrochloric acid. The aqueous layer was removed and the organic phase washed with saturated aqueous sodium bicarbonate, water and dried with brine and over sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate:petroleum ether (4:1 v/v) and neat ethyl acetate, to give the title compound as a colourless gum (1.22g).

Hplc system 1 (λ = 254nm) Rt 9.8min

Intermediate 53

3-({3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-phenyl-amino)-propionic acid

2M Aqueous sodium hydroxide (2.54ml) was added to a stirred solution of 3-({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-phenyl-amino)-propionic acid methyl ester (1.22g) in 1,4-dioxan (15ml). 2M Aqueous hydrochloric acid (2.54ml) was added after 16h. The reaction mixture was evaporated and the residue partitioned between ethyl acetate and water. The aqueous layer was removed and the organic phase was dried with brine and over sodium sulphate and then concentrated under reduced pressure to give the title compound (1.10g) as a white foam.

Mass spectrum: Found: MH^+ 540 (^{35}Cl)

Intermediate 54

(2-{3-Chloro-5-[(2-fluorosulfonyl-ethyl)-phenyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

2M Oxalyl chloride solution in dichloromethane (0.9ml) and DMF (0.025ml) were added to a suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.610g) in anhydrous dichloromethane (50ml). The reaction was stirred at room temperature for 1h then 2-phenylamino-ethanesulfonyl fluoride(0.257g), DMAP (0.018g) and DIPEA (0.261ml) were added. The reaction mixture was stirred at room temperature for 20h and partitioned between ethyl acetate and 1M aqueous hydrochloric acid. The aqueous layer was removed and the organic phase washed with saturated aqueous sodium bicarbonate, water and dried with brine and over sodium sulphate and concentrated under reduced

pressure. The residue was purified by flash column chromatography, eluting with using ethyl acetate:petroleum ether (3:1 v/v) to give the title compound as a white foam (0.40g)

Hplc system 1 (λ = 254nm) Rt 10.3min

Intemediate 55

3-[(3-Chloro-5-methoxy-benzoyl)-isopropyl-amino]-propionic acid methyl ester

To a stirred solution of 3-chloro-5-methoxy-benzoic acid (0.932g), TBTU (3.21g) and in DMF (10ml) was added DIPEA (1.73ml) followed by 3-isopropylamino propionic acid methyl ester (0.871g) after 10min. The reaction mixture was stirred at room temperature for 48h and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic phase was washed with further water and 2M aqueous sodium hydroxide, water and dried with brine and over sodium sulphate and concentrated under reduced pressure to give the title compound as a brown oil (1.6g).

Mass spectrum: Found: MH^+ 314

Intemediate 56

3-[(3-Chloro-5-methoxy-benzoyl)-isopropyl-amino]-propionic acid

2M Aqueous sodium hydroxide (4.5ml) was added to a stirred solution of 3-[(3-chloro-5-methoxy-benzoyl)-isopropyl-amino]-propionic acid methyl ester (1.50g) in 1,4-dioxan (30ml). 2M aqueous hydrochloric acid (4.5ml) was added after 20h. The reaction mixture was evaporated and the residue partitioned between ethyl acetate and water. The aqueous layer was removed and the organic phase was dried with brine and over sodium sulphate and then concentrated under reduced pressure to give the title compound (1.41g) as a brown solid.

Mass spectrum: Found: MH^+ 300 (^{35}Cl)

Intemediate 57

3-Chloro-N-isopropyl-5-methoxy-N-(2-methylcarbamoyl-ethyl)-benzamide

To a stirred solution of 3-[(3-chloro-5-methoxy-benzoyl)-isopropyl-amino]-propionic acid (0.600g), TBTU (1.28g) in DMF (10ml) was added DIPEA (0.696ml) followed a 2M solution of methylamine in THF (8.0ml) after 10min. The reaction mixture was stirred at room temperature for 4h and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic phase was washed with further water and 1M aqueous hydrochloric acid, saturated

aqueous sodium bicarbonate, water and dried with brine and over sodium sulphate and concentrated under reduced pressure to give the title compound as a brown oil (0.575g).

Mass spectrum: Found: MH^+ 313 (^{35}Cl)

Intemediate 58

3-Chloro-N-isopropyl-5-methoxy-N-[2-(1-methyl-1H-tetrazol-5-yl)-ethyl]-benzamide

To a stirred solution of 3-chloro-N-isopropyl-5-methoxy-N-(2-methylcarbamoyl-ethyl)-benzamide (0.312g) in anhydrous dichloromethane (5.0ml) was added sodium azide (0.065g) and the mixture cooled to 0°C. Trifluoromethanesulphonic anhydride (0.200ml) was added and the reaction stirred at rooom temperature for 18h. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was removed and the organic layer dried with brine and over sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate:petroleum ether (4:1 v/v); to give the title compound as a white solid (0.121g).

Hplc system 1 (λ = 254nm) Rt 8.2min

Intemediate 59

3-Chloro-5-hydroxy-N-isopropyl -N-[2-(1-methyl-1H-tetrazol-5-yl)-ethyl]-benzamide

To a stirred solution of 3-chloro-N-isopropyl-5-methoxy-N-[2-(1-methyl-1H-tetrazol-5-yl)-ethyl]-benzamide (0.115g) in anhydrous dichloromethane (5.0ml) at -78°C was added 1M boron tribromide solution in dichloromethane (1.36ml). The reaction mixture was stirred at this temperature for 15min. The reaction was allowed to warm to room temperature. After 24h, the reaction was cooled to -78°C and methanol (1ml) added. The reaction was allowed to rewarm to room temperature and absorbed on to silica. This was loaded on to an already prepared flash column, eluting with ethyl acetate:petroleum ether (4:1 v/v) and 25:1 dichloromethane:methanol (25:1 v/v) to give the title compound as a white solid (0.072g).

Hplc system 1 (λ = 254nm) Rt 6.6min

Intermediate 60

[2-(3-Chloro-5-[isopropyl-[2-(1-methyl-1H-tetrazol-5-yl)-ethyl]-carbamoyl)-phenoxy)-ethyl]-pyridin-4-yl-carbamic acid tert-butyl ester

To a solution of 3-chloro-5-hydroxy-N-isopropyl -N-[2-(1-methyl-1H-tetrazol-5-yl)-ethyl]-benzamide (0.070g) in DMF (2.0ml) stirred at room temperature under nitrogen was added sodium hydride (60% dispersion in oil, 0.010 g) and after 10min was added toluene-4-sulfonic acid 2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethyl ester (0.120g). The reaction was stirred for 88h and the sovent removed *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic phase was washed with further water and 1M aqueous sodium hydroxide, water and dried with brine and over sodium sulphate and concentrated under reduced pressure to give the crude product which was purified by flash column chromatography, eluting with ethyl acetate:petroleum ether (4:1 v/v) and 24:1 dichloromethane:methanol (24:1 v/v), to give the title compound as a colourless gum (0.028g).
Hplc system 1 (λ = 254nm) Rt 8.3min

Intermediate 61

(2-{3-Chloro-5-[cyclopentyl-(3-trifluoromethanesulfonylamino-propyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.059g), TBTU (0.072g), and HOBt (0.034g) in DMF (1ml) was added DIPEA (0.078ml) followed by N-(3-cyclopentylamino-propyl)-C,C,C-trifluoro-methanesulfonamide formate (0.053g) after 5min. The reaction mixture was stirred at room temperature for 4 days then more TBTU (0.072g), HOBt (0.034g) and DIPEA (0.078ml) were added followed by more of the secondary amine (0.06g). The mixture was heated to 60°C for 3h, the solvent was removed by evaporation at reduced pressure and the residue subjected to preparative hplc. This gave the title compound as a colourless gum (0.012g).
Hplc system 1 (λ = 254nm) Rt 12.5min

Intermediate 62

[2-{3-[2-(3-Amino-[1,2,4]oxadiazol-5-yl)-ethyl]-isopropyl-carbamoyl}-5-chloro-phenoxy)-ethyl]-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.104g), TBTU (0.128g), and HOBt (0.061g) in DMF (1ml) was added DIPEA (0.139ml) and 5-(2-isopropylamino-ethyl)-[1,2,4]oxadiazol-3-ylamine (0.05g). The reaction mixture was stirred at room temperature for 10 days, then silica was added and the solvent removed by evaporation at reduced pressure. The resulting silica was loaded onto the top of a column of silica which was then eluted

with a gradient [cyclohexane:ethyl acetate (1:1 v/v) to neat ethyl acetate to ethyl acetate:methanol (9:1 v/v)]. Concentration of the required fraction at reduced pressure furnished the title compound as a yellow glass (0.069g).
Hplc system 1 (λ = 254nm) Rt 8.2min

Intermediate 63

(2-{3-Chloro-5-[(2-cyano-ethyl)-cyclopropylmethyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g), TBTU (0.096g) and HOBt (0.030g) in DMF (1ml) was added DIPEA (0.052ml) followed by 3-(cyclopropylmethyl-amino)-propionitrile[4] (0.044g) after 15min. The reaction was stirred at room temperature for 14h, and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.070g) was obtained as a brown oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 499 (^{35}Cl)

Intermediate 64

(2-{3-Chloro-5-[(2-cyano-ethyl)-(2,2-dimethyl-propyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g), TBTU (0.096g) and HOBT (0.030g) in DMF (1ml) was added DIPEA (0.052ml) followed by 3-(2,2-dimethyl-propylamino)-propionitrile[5] (0.043g) after 15min. The reaction was stirred at room temperature for 18h, and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.053g) was obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 515 (^{35}Cl)

Intermediate 65

(2-{3-Chloro-5-[(2-cyano-ethyl)-(tetrahydro-furan-2-ylmethyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g), TBTU (0.096g) and HOBT (0.030g) in DMF (1ml) was

added DIPEA (0.052ml) followed by 3-[(tetrahydro-furan-2-ylmethyl)-amino]-propionitrile (0.047g) after 15min. The reaction was stirred at room temperature for 96h, and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.078g) was obtained as a brown oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 529 (^{35}Cl)

Intermediate 66

{2-[3-Chloro-5-[(2-cyano-ethyl)-isopropyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g), TBTU (0.096g) and HOBT (0.030g) in DMF (1ml) was added DIPEA (0.052ml) followed by 3-isopropylamino-propionitrile[6] (0.034g) after 15min. The reaction was stirred at room temperature for 96h, and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.072g) was obtained as a brown oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 487 (^{35}Cl)

Intermediate 67

{2-[3-Chloro-5-[(2-cyano-ethyl)-isobutyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g), TBTU (0.096g) and HOBT (0.030g) in DMF (1ml) was added DIPEA (0.052ml) followed by 3-isobutylamino-propionitrile[7] (0.038g) after 15min. The reaction was stirred at room temperature for 18h, and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.060g) was obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 501 (^{35}Cl)

Intermediate 68

3-({3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-isopropyl-amino)-propionic acid methyl ester trifluoroacetate

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.344g), TBTU (0.549g) and HOBT (0.173g) in DMF (6ml) was added DIPEA (0.296ml) followed by 3-isopropylamino-propionic acid methyl ester (0.254g) after 15min. The reaction was stirred at room temperature for 24h, and then concentrated under reduced pressure. The residue was partitioned between saturated sodium bicarbonate solution and ethyl acetate. The aqueous layer was separated and extracted with further ethyl acetate. The combined, dried ($MgSO_4$) organic fractions were concentrated under reduced pressure. The residue was subjected to preparative hplc to give the title compound (0.332g) as a colourless oil, by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 1 (λ = 254nm) Rt 9.7min

Intermediate 69

3-({3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-isopropyl-amino)-propionic acid hydrochloride

To a solution of 3-({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-isopropyl-amino)-propionic acid methyl ester trifluoroacetate (0.33g) in dioxan (3ml) was added 2M sodium hydroxide 0.95ml, and the resultant solution was stirred at room temperature for 3h. 1M Hydrochloric acid (*ca.* 4ml) was added and the resultant suspension extracted with ethyl acetate. The combined, dried ($MgSO_4$) extracts were concentrated under reduced pressure to give the title compound (0.201g) as a colourless oil.
Mass spectrum: Found: MH^+ 506 (^{35}Cl)

Intermediate 70

{2-[3-Chloro-5-[(2-diethylcarbamoyl-ethyl)-isopropyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester trifluoroacetate

To a stirred solution of 3-({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-isopropyl-amino)-propionic acid hydrochloride (0.052g), TBTU (0.064g) and HOBT (0.027g) in DMF (1ml) was added DIPEA (0.035ml) followed diethylamine (0.021ml) after 15min. The reaction was stirred at room temperature for 3 days, and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.065g) was obtained as a

colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure

Mass spectrum: Found: MH^+ 561 (^{35}Cl)

Intermediate 71

1-{3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-piperidine-2-carboxylic acid ethyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.12g) in dichloromethane (4ml) was added dimethylformamide (0.05ml) followed by 2M oxalyl chloride solution in dichloromethane (0.183ml). The resultant solution was stirred at room temperature for 1h, and then ethyl pipecolinate (0.096g) followed by DIPEA (0.160ml) were added. After 18h, the reaction mixture was concentrated under reduced pressure and the residue was subjected to preparative hplc. The title compound (0.165g) was obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Mass spectrum: Found: MH^+ 532 (^{35}Cl)

Intermediate 72

{2-[3-Chloro-5-(2-methyl-piperidine-1-carbonyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g) in dichloromethane (4ml) was added DMF (0.025ml) followed by 2M oxalyl chloride solution in dichloromethane (0.091ml). The resultant solution was stirred at room temperature for 1h, and then 2-methylpiperidine (0.03g) followed by DIPEA (0.080ml) were added. After 3h, the solution was concentrated under reduced pressure and the residue was subjected to preparative hplc. The title compound (0.080g) was obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 10.4min

Intermediate 73

{2-[3-Chloro-5-[(2-cyano-ethyl)-cyclopentyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.100g), TBTU (0.080g) and HOBt (0.034g) in DMF (3ml) was added DIPEA (0.087ml) followed by 3-(cyclopentylamino)propionitrile (0.035g) after 15min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was washed with water and extracted with ethyl acetate. The organic layer was dried with brine and $MgSO_4$, filtered and concentrated to give the title compound (0.190g) as a brown oil.

Mass spectrum: Found: MH^+ 513 (^{35}Cl).

Intermediate 74

{2-{3-Chloro-5-[isopropyl-(2-[1,2,4]triazol-1-yl-ethyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.1g) in DMF (1ml)and dichloromethane (3ml),was added 2M oxalyl chloride in dichloromethane (0.153ml) and after 30min, a catalytic amount of DMAP and DIPEA (0.013ml), followed by 2-(2-isopropylamino-ethyl)-N-[1,2,4]-triazole (0.038g). The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was washed with water and extracted with ethyl acetate. The organic layer was dried with brine and $MgSO_4$, filtered and concentrated to give the title compound (0.097g) as a brown oil.

Mass spectrum: Found: MH^+ 529 (^{35}Cl)

Intermediate 75

{2-{3-[(3-Amino-propyl)-isopropyl-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

A solution of (2-{3-chloro-5-[(-cyano-ethyl)-isopropyl-carbamoyl]-phenoxy)-ethyl)-pyridin-4yl-carbamic acid tert-butyl ester (0.200g) in methanol (2ml) at 0°C was treated with cobalt (II) chloride hexahydrate (0.195g) and sodium borohydride (0.078g) and stirred overnight at room temperature. Silica was added and the mixture was evaporated under reduced pressure, the residue was subjected to flash chromatography eluting with methanol:chloroform:ammonia(0.88) (10:89:1 v/v/v). The required fractions were evaporated under reduced pressure to give the title compound as a pale straw coloured oil (0.128g).

Hplc system 1 (λ =254nm) Rt 6.5min

Intermediate 76

{2-[3-Chloro-5-[isopropyl-(3-trifluoromethanesulfonylamino-propyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester trifluoroacetate

To a solution of (2-{3-[(3-amino-propyl)-isopropyl-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.044g) and triethylamine (0.024ml) in dichloromethane (1ml) at -70°C was added trifluoromethanesulphonic anhydride (0.016ml), and the mixture was stirred overnight at room temperature. The mixture was diluted with dichloromethane(4ml) and washed with saturated sodium bicarbonate(2ml), dried (sodium sulphate) and evaporated under reduced pressure. The residue was subjected to preparative hplc to give the title compound (0.022g).

Hplc system 1 (λ= 254nm) Rt 11.4min

Intermediate 77

{2-[3-Chloro-5-(2,5-dimethyl-pyrrolidine-1-carbonyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

2,5-Dimethylpyrrolidine (0.14ml) in DMF (1ml) was added to a mixture of 3-[2-(tert-butoxycarbonyl-pyridin-4yl-amino)ethoxy]-5-chlorobenzoic acid (0.30g), HOBT (0.10g), TBTU (0.37g), and DIPEA (0.30ml) in DMF (1ml) and stirred overnight at room temperature. The mixture was diluted with water, extracted with ether, the ether layer was washed with water, brine, dried over sodium sulphate and evaporated under reduced pressure. The residue was subjected to flash chromatography eluting with ethyl acetate:cyclohexane (80:20 v/v) to give the title compound as an oil (0.27g).

Tlc Rf(Silica gel 60 F_{254}) = 0.2 [ethyl acetate:cyclohexane (80:20 v/v)]

Intermediate 78

[2-(3-chloro-5-{[3-(2,2-dimethyl-propionylamino)-propyl]-isopropyl-carbamoyl}-phenoxy)-ethyl]-pyridine-4-yl-carbamic acid tert-butyl ester

To a solution of (2-{3-[(3-amino-propyl)-isopropyl-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.040g) and DIPEA (0.030ml) in dichloromethane (1ml) was added a solution of trimethylacetyl chloride (0.012ml) in dichloromethane (1ml) and the mixture was stirred for 3h at room temperature. The mixture was evaporated under reduced pressure to give the title compound.

Hplc system 1 (λ= 254nm) Rt 10.3min

Intermediate 79

{2-[3-Chloro-5-(cyclopentyl-(2-[1,2,4]triazol-1-yl-ethyl)-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

A solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.040g), cyclopentyl-(2-[1,2,4]triazol-1-yl-ethyl)-amine (0.05g) and EEDQ (0.040g) in acetonitrile (2ml) was stirred at reflux, under nitrogen, for 2h. The solvent was evaporated and the residue was purified by flash chromatography eluting with dichloromethane:methanol (95:5 v/v) to give the title compound as a yellow oil (0.022g).

Mass spectrum: Found: MH^+ 555

Intermediate 80

{2-[3-Chloro-5-(cyclopentyl-(4-[1,2,4]triazol-1-yl-butyl)-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

A solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.040g), cyclopentyl -(4-[1,2,4]triazol-1-yl-butyl)-amine (0.055g) and EEDQ (0.050g) in acetonitrile (2ml) was stirred at reflux, under nitrogen, for 4h. The solvent was evaporated and the residue was purified by flash chromatography eluting with dichloromethane:methanol:ammonia (95:5:0.5 then 90:10:1 v/v/v) to give the title compound as an orange oil (0.022g).

Mass spectrum: Found: MH^+ 583 (^{35}Cl)

Intermediate 81

{2-[3-Chloro-5-(3-fluorophenyl-(3-tetrazol-2-yl-propyl)-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

2M Oxalyl chloride solution in dichloromethane (0.11ml) and dry DMF (0.002ml) were added to a stirred suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g) in dry dichloromethane (1ml) under nitrogen. After 5min, DIPEA (0.090ml) was added followed after a further 40min by 3-fluorophenyl-(3-tetrazol-2-yl-propyl)-amine (0.066g) and DMAP (0.002g). After 3 days the solvent was evaporated and the residue was purified by flash chromatography eluting with dichloromethane:methanol (98:2 v/v) to give the title compound as a green foam (0.079g).

Mass spectrum: Found: MH^+ 596 (^{35}Cl)

Intermediate 82

{2-[3-Chloro-5-(2-fluorophenyl-(3-tetrazol-2-yl-propyl)-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

2M Oxalyl chloride solution in dichloromethane (0.110ml) and dry DMF (0.002ml) were added to a stirred suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.060g) in dry dichloromethane (1ml) under nitrogen. After 5min DIPEA (0.090ml) was added followed after a further 40min by 2-fluorophenyl-(3-tetrazol-2-yl-propyl)-amine (0.066g) and DMAP (0.002g). After 40h the solvent was evaporated and the residue was purified by flash chromatography, eluting with dichloromethane:methanol (98:2 v/v) to give the title compound as a viscous yellow oil (0.059g).

Mass spectrum: Found: MH^+ 596 (^{35}Cl)

Intermediate 83

{2-[3-Chloro-5-(phenyl-(3-tetrazol-2-yl-propyl)-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

2M Oxalyl chloride solution in dichloromethane (0.11ml), and dry DMF (0.005ml) were added to a stirred suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.067g) in dry dichloromethane (1ml) under nitrogen. After 10min, DIPEA (0.100ml) was added followed after a further 40min by phenyl-(3-tetrazol-2-yl-propyl)-amine (0.033g) and DMAP (0.004g). After 7 days the solvent was evaporated and the residue was purified by flash chromatography, eluting with dichloromethane:methanol (98:2 v/v) to give the title compound as a pale yellow oil (0.024g).

Mass spectrum: Found: MH^+ 564 (^{35}Cl)

Intermediate 84

{2-[3-Chloro-5-(phenyl-(3-[1,2,3]-triazol-2-yl-propyl)-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

2M Oxalyl chloride solution in dichloromethane (0.25ml) and dry DMF (0.010ml) were added to a stirred suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.161g) in dry dichloromethane (2ml) under nitrogen. After 10min. DIPEA (0.25ml) was added followed after a further 40min by phenyl-(3-[1,2,3]-triazol-2-yl-propyl)-amine (0.077g) and DMAP (0.012g). After 7 days the solvent was evaporated and the residue was purified by flash chromatography, eluting with dichloromethane:methanol (96:4 v/v) to give the title compound as a yellow oil (0.083g).

Mass spectrum: Found: MH^+ 563 (^{35}Cl)

Intermediate 85

{2-[3-Chloro-5-(phenyl-2-(pyridin-2-yloxy)-ethyl-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

2M Oxalyl chloride in dichloromethane (0.16ml) and dry DMF (0.008ml) were added to a stirred suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.115g) in dry dichloromethane (1.5ml) under nitrogen. After 10min, DIPEA (0.18ml) was added followed after a further 40min by phenyl-2-(pyridin-2-yloxy)-ethylamine (0.059g) and DMAP (0.008g). After 7 days the solvent was evaporated and the residue was purified by flash chromatography, eluting with dichloromethane:methanol (98:2 v/v), to give the title compound as a pale yellow oil (0.065g).

Mass spectrum: Found: MH^+ 589 (^{35}Cl)

Intermediate 86

{2-[3-Chloro-5-(isopropyl-2-methoxy-ethyl-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

A solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.100g) isopropyl-2-methoxy-ethylamine (0.140g) and EEDQ (0.130g) in acetonitrile (2ml) was stirred at 50°C, under nitrogen, for 18h. The solvent was evaporated and the residue was partitioned between water and ethyl acetate. The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated to an orange oil which was purified by flash chromatography, eluting with dichloromethane:methanol (98:2 then 96:4 v/v) to give the title compound as a pale yellow oil (0.065g).

Mass spectrum: Found: MH^+ 492 (^{35}Cl)

Intermediate 87

{2-[3-Chloro-5-(isopropyl-methyl-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.071g), TBTU (0.064g), and HOBt (0.03g) in DMF (1ml) was added N-isopropylmethylamine (0.095ml) after 25min. The reaction mixture was stirred at room temperature for 2 days then the solvent was removed by evaporation at reduced pressure and the residue partitioned between ethyl acetate and water.

The combined organic layers were washed with saturated brine and dried over magnesium sulphate. After concentration, the crude product was purified by flash chromatography eluting with ethyl acetate. Evaporation of the required fraction at reduced pressure gave the title compound as a pale yellow gum (0.065g).
Hplc system 3 (λ = 220-330nm) Rt 4.2min

Intermediate 88
{2-[3-Chloro-5-(isopropyl-2-(pyridin-2-yloxy)-ethyl-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester
A solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.10g) isopropyl-2-(pyridin-2-yloxy)-ethylamine (0.18g) and EEDQ (0.136g) in acetonitrile (2ml) was stirred at reflux, under nitrogen, for 18h. The solvent was evaporated and the residue was purified by flash chromatography on silica eluting with dichloromethane/methanol (98:2 then 96:4) to give the title compound as a pale yellow oil (0.033g).
Mass spectrum: Found: MH^+ 555 (^{35}Cl)

Intermediate 89
{2-[3-Chloro-5-(diisopropylcarbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester
To a suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.10g) in tetrahydrofuran (5ml) was added DMF (0.005ml) and oxalyl chloride (0.175ml). After 0.5h DIPEA (0.13ml), diisopropylamine (0.20ml) and DMAP (0.002g) were added. After 18h the mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The combined organic phases were washed with brine and dried over magnesium sulphate. Filtration and evaporation gave the crude product which was purified by flash column chromatography on silica eluting with cyclohexane/ethyl acetate (1:3). This afforded the title compound as a colourless gum (0.078g).
Mass spectrum: Found: MH^+ 476.2304 $C_{25}H_{35}{}^{35}ClN_3O_4$ requires 476.2316

Intermediate 90
3-[2-(Benzyloxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid methyl ester
A solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid methyl ester (0.950g) in dichloromethane (16ml) and trifluoroacetic acid (4ml)

was stored at room temperature for 1h. The solution was concentrated *in vacuo* and residual trifluoroacetic acid removed by co-evaporation with further dichloromethane. The residue was dissolved in dichloromethane (20ml) and the solution stirred with saturated aqueous sodium bicarbonate (25ml). Benzyl chloroformate (0.394ml) was added to the bi-phasic mixture and stirring continued for 20h. The aqueous layer was removed and the organic layer washed with 1M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, water and dried with brine and over sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate:petroleum ether (3:1 v/v), to give the title compound as a colourless gum (0.32g).
Hplc system 1 (λ = 254nm) Rt 10.6min

Intermediate 91
3-[2-(Benzyloxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid
To a stirred solution of 3-[2-(benzyloxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid methyl ester (0.32g) in a mixture of 1,4-dioxane (10ml) and water (5ml) was added 2M sodium hydroxide solution (0.72ml). The reaction mixture was stirred at room temperature for 20h, neutralised by the addition of 2M hydrochloric acid (0.72ml) and then concentrated under reduced pressure. The residue was triturated with water and then dissolved in a mixture of ethyl acetate, chloroform, tetrahydrofuran and methanol until all the gum had dissoved. The solution was dried over sodium sulphate and then concentrated under reduced pressure gave the title compound as a white solid (0.27g).
Hplc system 1 (λ = 254nm) Rt 8.1min

Intermediate 92
3-{(3-[2-(Benzyloxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl)-tert-butyl-amino)-propionic acid methyl ester
To a stirred suspension of 3-[2-(benzyloxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.265g)and DMF (0.010ml) in anhydrous dichloromethane (15ml) was added a 2M solution of oxalyl chloride in dichloromethane (0.434ml). After 1h a mixture of 3-(tert-butylamino)-propionic acid methyl ester (0.987g), DIPEA (0.324ml) and DMAP (0.008g) in dichloromethane (5ml) was added and the reaction stirred at room temperature for 18h. The reaction mixture was diluted with chloroform:dichloromethane (1:1 v/v, 50ml) and extracted with 2M aqueous sodium

hydroxide, 2M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and dried with brine and over sodium sulphate. The solvent was evaporated under reduced pressure and the residue purified by flash column chromatography, eluting with ethyl acetate:petroleum ether (2:1 and 3:1 v/v) to give the title compound as a colourless gum (0.038g).
Hplc system 1 (λ = 254nm) Rt 10.5min

Intermediate 93
3-({3-[2-(Benzyloxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-tert-butyl-amino)-propionic acid
To a stirred solution of 3-({3-[2-(benzyloxycarbonyl-pyridin-yl-amino)-ethoxy]-5-chloro-benzoyl}-tert-butyl-amino)-propionic acid methyl ester (0.038g) in a mixture of 1,4-dioxane (1ml) and water (0.5ml) was added 2M sodium hydroxide solution (0.066ml). The reaction mixture was stirred at room temperature for 1h, neutralised by the addition of 2M hydrochloric acid (0.066ml) and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and brine, the aqueous layer was removed and the organic layer was dried over sodium sulphate and then concentrated under reduced pressure gave the title compound as a white solid (0.034g).
Hplc system 1 (λ = 254nm) Rt 8.5min

Intermediate 94
{2-{3-[tert-Butyl-(2-tert-butylcarbamoyl-ethyl)-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid benzyl ester
A solution of 3-({3-[2-(benzyloxycarbonyl-pyridin-yl-amino)-ethoxy]-5-chloro-benzoyl}-tert-butyl-amino)-propionic acid (0.034g), HATU® (0.046g) and DIPEA (0.020ml) was stirred for 20min then tert-butylamine (0.063ml) was added. After 14h the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The aqueous layer was removed and the organic layer washed with further water, 1M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, water and dried with brine and over sodium sulphate. The solvent was removed to give the title compound as a colourless gum (0.024g).
Hplc system 1 (λ = 254nm) Rt 8.5min

Intermediate 95

3-({3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-cyclobutyl-amino)-propionic acid methyl ester compound
To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.196g) and TBTU (0.321g) in DMF (5ml) was added DIPEA (0.174ml) followed by 3-(cyclobutyl-amino)-propionic acid methyl ester (0.314g) after 10min. The reaction mixture was stirred at room temperature for 68h and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The aqueous layer was removed and the organic layer washed with further water, saturated aqueous sodium bicarbonate, 1M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and water. The organic layer was dried with brine and over sodium sulphat. The solvent was removed under reduced pressure and the residue purified by flash column chromatography, eluting with ethyl acetate:petroleum ether (2:1 v/v), to give the title compound (0.096g) as a colourless gum.
Mass spectrum: Found: MH^+ 532 (^{35}Cl)

Intermediate 96
3-({3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-cyclobutyl-amino)-propionic acid
To a stirred solution of 3-({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-cyclobutyl-amino)-propionic acid methyl ester (0.096g) in a mixture of 1,4-dioxane (2ml) and water (1ml) was added 2M sodium hydroxide solution (0.180ml). The reaction mixture was stirred at room temperature for 2h, neutralised by the addition of 2M hydrochloric acid (0.180ml) and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water, the aqueous layer removed and the organic layer extracted with 0.2M sodium hydroxide. The aqueous layer was acidified with an equivalent volume of 0.2M hydrochloric acid, and extracted with ethyl acetate. This solution was dried over sodium sulphate and then concentrated under reduced pressure gave the title compound as a colourless gum (0.050g).
Hplc system 1 (λ = 254nm) Rt 8.2min

Intermediate 97
{2-{3-[(2-tert-Butylcarbamoyl-ethyl)-cyclobutyl-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester

To a stirred solution of ({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-cyclobutyl-amino)-propionic acid (0.025g) and HATU® (0.038g) in DMF (1ml) was added DIPEA (0.017ml) followed by tert-butylamine (0.053ml) after 10min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.021g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 573 (^{35}Cl)

Intermediate 98
[2-{3-Chloro-5-{cyclobutyl-[2-(2,2-dimethyl-propylcarbamoyl)-ethyl]-carbamoyl}-phenoxy)-ethyl]-pyridin-4-yl-carbamic acid tert-butyl ester
To a stirred solution of ({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-cyclobutyl-amino)-propionic acid (0.025g) and HATU® (0.038g) in DMF (1ml) was added DIPEA (0.017ml) followed by neopentylamine (0.053ml) after 10min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.016g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 587 (^{35}Cl)

Intermediate 99
(2-{3-Chloro-5-[(2-cyano-ethyl)-cyclobutyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester
To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.030g) and HATU® (0.058g) in DMF (0.4ml) was added DIPEA (0.040ml) followed by a solution of 3-(cyclobutylamino)propionitrile (0.038g) in DMF (0.6ml) after 10min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.042g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 499 (^{35}Cl)

Intermediate 100
(2-{3-Chloro-5-[isopropyl-(2-sulfamoyl-ethyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester
To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.030g) and HATU® (0.058g) in DMF (0.4ml) was added DIPEA (0.040ml) followed by a solution of 2-isopropylamino-ethanesulfonic acid amide (0.058g) in DMF (0.6ml) after 10min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.012g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 541 (^{35}Cl)

Intermediate 101
[2-{3-Chloro-5-{[2-(2,2-dimethyl-propylsulfamoyl)-ethyl]-isopropyl-carbamoyl}-phenoxy)-ethyl]-pyridin-4-yl-carbamic acid tert-butyl ester
To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.030g) and HATU® (0.058g) in DMF (0.4ml) was added DIPEA (0.040ml) followed by a solution of 2-isopropylamino-ethanesulfonic acid (2,2-dimethyl-propyl)-amide (0.070g) in DMF (0.6ml) after 10min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.042g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Mass spectrum: Found: MH^+ 611 (^{35}Cl)

Intermediate 102
3-Chloro-N{2-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-ethyl}-N-isopropyl-5-[2[(pyridin-4-ylamino)-ethoxy]-benzamide carbamic acid tert-butyl ester
To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.100g), TBTU (0.164g) in DMF (3ml) was added DIPEA (0.174ml) followed by (3-(2-isopropylamino-ethyl)-5-hydroxy-[1,2,4]oxadiaxole trifluoroacetate (0.043g) after 15 min. The reaction mixture was stirred at room

temperature for 18h and then concentrated under reduced pressure and the residue subjected to preparative hplc to give the title compound (0.046g) as a colourless oil.
Mass spectrum: Found: MH^+ 546 (^{35}Cl)

Intermediate 103
[2-[3-Chloro-5-(isopropyl-(2-(4-tert-butylphenyl)-ethyl-carbamoyl)-phenoxy]-ethyl]-pyridin-4-yl-carbamic acid tert-butyl ester
A solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.100g), isopropyl-2-(4-*tert*-butylphenyl)-ethylamine (0.170g) and EEDQ (0.136g) in acetonitrile (2ml) was stirred at reflux, under nitrogen, for 6h. The solvent was evaporated and the residue was purified by flash chromatography, eluting with dichloromethane:methanol (98:2 v/v), to give the title compound as a pale yellow oil (0.063g).
Mass Spectrum: Found: MH^+ 594 (^{35}Cl)

Example 1
N-Cyclohexyl-3,N-dimethyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate salt
A stirred solution of 3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoic acid trifluoroacetate salt (0.031g) in DMF (1ml) was treated with HOBt (0.011g), DIPEA (0.028ml), N-methylcyclohexylamine (0.010ml), and TBTU (0.026g). The resulting solution was retained in a sealed flask for 64h. The reaction mixture was concentrated under reduced pressure and the resulting gum subjected to preparative hplc. The required fraction was concentrated and then dried by addition of methanol and concentration under reduced pressure, addition of toluene and again concentration under reduced pressure giving the title compound as a colourless gum (0.034g).
Hplc system 2 (λ = 254nm) Rt 11.6min
Mass spectrum: Found: MH^+ 368.2336 $C_{22}H_{30}N_3O_2$ requires 368.2338

Example 2
3-Bromo-N-cyclohexyl-N-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate salt
To a stirred solution of 3-bromo-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoic acid trifluoroacetate salt (0.034g), TBTU (0.048g) and HOBt (0.014g) in DMF (0.3ml) was added DIPEA (0.026ml) followed by N-methylcyclohexylamine (0.020ml) after

15min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.005g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 2 (λ = 254nm) Rt 12.0min
Mass spectrum: Found: MH^+ 432 (^{79}Br)

Example 3
N-Allyl-3-bromo-N-cyclohexyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate salt
To a stirred solution of 3-bromo-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoic acid trifluoroacetate salt (0.034g), TBTU (0.048g) and HOBt (0.014g) in DMF (0.3ml) was added DIPEA (0.026ml) followed by N-allylcyclohexylamine (0.022ml) after 15min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.011g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 2 (λ = 254nm) Rt 12.8min
Mass spectrum: Found: MH^+ $C_{23}H_{29}{}^{79}Br_1N_3O_2$ requires 458.1443

Example 4
N-Allyl-3-bromo-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate salt
To a stirred solution of 3-bromo-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoic acid trifluoroacetate salt (0.034g), TBTU (0.048g) and HOBt (0.014g) in DMF (0.3ml) was added DIPEA (0.026ml) followed by N-allylcyclopentyamine (0.022ml) after 15min. The reaction mixture was stirred at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.022g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 2 (λ = 254nm) Rt 12.4min
Mass spectrum: Found: MH^+ $C_{22}H_{27}{}^{79}Br_1N_3O_2$ requires 444.1287

Example 5

3-Chloro-N-cyclohexyl-N-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate salt

A solution of {2-[3-chloro-5-(cyclohexyl-methyl-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.036g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 2h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.024g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 8.1min

Mass spectrum: Found: MH^+ $C_{21}H_{27}{}^{35}Cl_1N_3O_2$ requires 388.1792

Example 6

N-Allyl-3-chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate salt

A solution of {2-[3-(allyl-cyclopentyl-carbamoyl)-5-chloro-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.030g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 2h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.026g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 8.7min

Mass spectrum: Found: MH^+ 400 (^{35}Cl)

Example 7

N-Allyl-3-chloro-N-cyclohexyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate salt

A solution of {2-[3-(allyl-cyclohexyl-carbamoyl)-5-chloro-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.032g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 2h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.027g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 9.3min

Mass spectrum: Found: MH^+ 414.1960 $C_{23}H_{29}{}^{35}Cl_1N_3O_2$ requires 414.1962

Example 8

3-Chloro-N-cyclohexyl-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate salt

A solution of {2-[3-(propyl -cyclopentyl-carbamoyl)-5-chloro-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.07g) in a mixture of dichloromethane (2ml) and trifluoroacetic acid (2ml) was stored at room temperature for 1h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.036g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 9.2min

Mass spectrum: Found: MH^+ 402.1952 $C_{22}H_{28}{}^{35}Cl_1N_3O_2$ requires 402.1948

Example 9

3-Chloro-N-cyclopentyl-N-(3-hydroxy-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[cyclopentyl-(3-hydroxy-propyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.07g) in a mixture of dichloromethane (2ml) and trifluoroacetic acid (2ml) was stored at room temperature for 1h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.011g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 6.9min

Mass spectrum: Found: MH^+ 418 (^{35}Cl)

Example 10

3-Chloro-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(tetrahydro-pyran-4-yl)-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[propyl-(tetrahydro-pyran-4-yl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.070g) in a mixture of dichloromethane (2ml) and trifluoroacetic acid (2ml) was stored at room temperature for 2h and then concentrated under reduced pressure. The residue was subjected

to preparative hplc and the title compound (0.048g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 1 (λ = 254nm) Rt 6.9min
Mass spectrum: Found: MH^+ 418.1882 $C_{27}H_{29}{}^{35}Cl_1N_3O_3$ requires 418.1897

Example 11
{[3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl)-cyclopentyl-amino)-acetic acid
To a solution of (2-[3-(allyl-cyclopentyl-carbamoyl)-5-chloro-phenoxy)-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.06g) in tert-butanol (3.2ml) was added a solution of potassium permanganate (0.006g), sodium periodate (0.157g) and sodium bicarbonate (0.051g) in water (3.2ml). The purple reaction mixture was stirred at room temperature for 1.5h and then added to ethanol (25ml) the precipitate was filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in a mixture of dichloromethane (5ml) and trifluoroacetic acid (5ml) was stored at room temperature for 17h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.021g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure.
Hplc system 1 (λ = 254nm) Rt 6.7min
Mass spectrum: Found: MH^+ 418.1548 $C_{21}H_{25}{}^{35}Cl_1N_3O_4$ requires 418.1534

Example 12
3-Chloro-N-cyclopentyl-N-(2,3-dihydroxy-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate
A solution of crude (2-{3-chloro-5-[cyclopentyl-(2,3-dihydroxy-propyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.044g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 1h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.007g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 1 (λ = 254nm) Rt 6.2min
Mass spectrum: Found: MH^+ 434.1862 $C_{22}H_{29}{}^{35}Cl_1N_3O_4$ requires 434.1847

Example 13

3-Chloro-N-cyclopentyl-N-(3-morpholin-4-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide bis(trifluoroacetate)
A solution of (2-{3-chloro-5-[cyclopentyl-(3-morpholin-4-yl-propyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester trifluoroacetate (0.060g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 2h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.034g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 1 (λ= 254nm) Rt 6.4min
Mass spectrum: Found: MH^+ 487.2472 $C_{25}H_{36}{}^{35}Cl_1N_4O_3$ requires 487.2476

Example 14
3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-pyrrolidin-1-yl-propyl)-benzamide bis(trifluoroacetate)
A solution of (2-{3-chloro-5-[cyclopentyl-(3-pyrrolidin-1-yl-propyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester trifluoroacetate (0.080g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 2h and then concentrated under reduced pressure to give the title compound (0.075g) as a colourless gum.
Hplc system 1 (λ= 254nm) Rt 6.6min
Mass spectrum: Found: MH^+ 471.2514 $C_{26}H_{36}{}^{35}Cl_1N_4O_2$ requires 471.2527

Example 15
3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-pyrrolidin-1-yl-propyl)-N-(tetrahydro-pyran-4-yl)-benzamide bis(trifluoroacetate)
To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.059g), TBTU (0.085g) and HOBt (0.020g) in DMF (0.6ml) was added DIPEA (0.052ml) followed by N-(3-pyrrolidin-1-yl-propyl)-4-aminotetrahydropyran (0.048g) after 20min. The reaction mixture was stirred at room temperature for 20h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the product (0.005g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure. A solution of this product in trifluoroacetic acid (2ml) was stored at room

temperature for 18h and the solvent removed under reduced pressure to give the title compound (0.005g) as a colourless gum.
Hplc system 1 (λ= 254nm) Rt 5.6min
Mass spectrum: Found: MH^+ 487 (^{35}Cl)

Example 16

3-Chloro-N-(3-morpholin-4-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(tetrahydro-pyran-4-yl)-benzamide bis(trifluoroacetate)

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.059g), TBTU (0.085g) and HOBt (0.020g) in DMF (0.6ml) was added DIPEA (0.052ml) followed by N-(3-morpholin-4-yl-propyl)-4-aminotetrahydropyran (0.051g) after 20min. The reaction mixture was stirred at room temperature for 20h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the and the product (0.062g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure. A solution of this product in TFA (2ml) was stored at room temperature for 18h and the solvent removed under reduced pressure to give the title compound (0.060g) as a colourless gum.
Hplc system 1 (λ= 254nm) Rt 4.9min
Mass spectrum: Found: MH^+ 503 (^{35}Cl)

Example 17

4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclopentyl-amino)-butyric acid ethyl ester trifluoroacetate

A solution of crude 4-({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-cyclopentyl-amino)-butyric acid ethyl ester (0.020g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 2h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.005g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 1 (λ= 254nm) Rt 9.1min
Mass spectrum: Found: MH^+ 474.2172 $C_{25}H_{32}{}^{35}Cl_1N_3O_4$ requires 474.2160

Example 18

4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclopentyl-amino)-butyric acid

A solution of 4-({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-cyclopentyl-amino)-butyric acid (0.015g) in trifluoroacetic acid (3ml) was stored at room temperature for 2h and then the solvent removed under reduced pressure. The residue was purified by preparative hplc to give title compound (0.09g) as a colourless gum.
Hplc system 3 (λ= 220nm) Rt 3.7min
Mass spectrum: Found: MH^+ 446 (^{35}Cl)

Example 19

N-(3-Carbamoyl-propyl)-3-chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-[(3-carbamoyl-propyl)-cyclopentyl-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.040g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 2h and then concentrated under reduced pressure to give the title compound (0.040g) as a colourless gum.
Hplc system 1 (λ= 254nm) Rt 6.7min
Mass spectrum: Found: MH^+ 445.1989 $C_{23}H_{30}{}^{35}Cl_1N_4O_3$ requires 445.2006

Example 20

3-Chloro-N-cyclopentyl-N-(4-oxo-4-pyrrolidin-1-yl-butyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide bis(trifluoroacetate)

A solution of (2-{3-chloro-N-cyclopentyl-N-(4-oxo-4-pyrrolidin-1-yl-butyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.025g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 2h and then concentrated under reduced pressure to give the title compound (0.025g) as a colourless gum.
Hplc system 1 (λ = 254nm) Rt 8.5min
Mass spectrum: Found: MH^+ 499 (^{35}Cl)

Example 21

N-(2-Carbamoyl-ethyl)-3-chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-[(2-carbamoyl-ethyl)-cyclopentyl-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.074g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 2h and then concentrated under reduced pressure to give the title compound (0.060g) as a colourless gum.

Hplc system 1 (λ = 254nm) = 254nm) Rt 6.2min

Mass spectrum: Found: MH^+ 431.1857 $C_{22}H_{28}{}^{35}Cl_1N_4O_3$ requires 431.1830

Example 22

N-Carbamoylmethyl-3-chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-[(2-carbamoyl-methyl)-cyclopentyl-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.064g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 2h and then concentrated under reduced pressure to give the title compound (0.057g) as a colourless gum.

Hplc system 1 (λ = 254nm) Rt 6.0min

Mass spectrum: Found: MH^+ 417.1703 $C_{21}H_{26}{}^{35}Cl_1N_4O_3$ requires 417.1693

Example 23

N-(2-Carbamoyl-ethyl)-3-chloro-N-cyclopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide hydrochloride

A solution of (2-{3-chloro-5-[(2-cyano-ethyl)-cyclopropyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.075g) in a mixture of dichloromethane (5ml) and trifluoroacetic acid (5ml) was stored at room temperature for 18h and then concentrated under reduced pressure. The residue was triturated with ethereal hydrogen chloride to give the title compound (0.065g) as a colourless gum.

Hplc system 1 (λ = 254nm) Rt 5.1min

Mass spectrum: Found: MH^+ 417.1532 $C_{20}H_{24}{}^{35}Cl_1N_4O_3$ requires 417.1537

Example 24

N-(2-Carbamoyl-ethyl)-3-chloro-N-(1-propyl-butyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.118g), TBTU (0.170g) and HOBt (0.040g) in DMF (0.6ml) was added DIPEA (0.104ml) followed by N-(2-propylbutyl)-3-amino-propionamide

(0.086g) after 15min. The reaction mixture was stirred at room temperature for 20h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the product (0.005g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure. A solution of this product in triflouroacetic acid (2ml) was stored at room temperature for 18h and the solvent removed under reduced pressure to give the title compound (0.090g) as a colourless gum.

Hplc system 1 (λ = 254nm) Rt 7.6min

Mass spectrum: Found: MH^+ 461 (^{35}Cl)

Example 25

3-Chloro-N,N-dipropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide hydrochloride

A solution of [2-(3-chloro-5-dipropylcarbamoyl-phenoxy)-ethyl]-pyridin-4-yl-carbamic acid tert-butyl ester (0.085g) in a mixture of dichloromethane (2ml) and trifluoroacetic acid (2ml) was stored at room temperature for 18h and then concentrated under reduced pressure. The residue was triturated with ethereal hydrogen chloride to give the title compound (0.063g) as a colourless gum.

Hplc system 1 (λ = 254nm) Rt 7.9min

Mass spectrum: Found: MH^+ 376.1782 $C_{20}H_{27}{}^{35}Cl_1N_3O_2$ requires 376.1792

Example 26

3-Chloro-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[1,3,4]thiadiazol-2-yl-benzamide trifluoroacetate

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.050g), TBTU (0.074g) and HOBt (0.018g) in DMF (0.9ml) was added DIPEA (0.045ml) followed by N-propyl-2-amino-[1,3,4]thiadiazole (0.037g) after 15min. The reaction mixture was stirred at room temperature for 20h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the product (0.007g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure. A solution of this product in trifluoroacetic acid (2ml) was stored at room temperature for 18h and the solvent removed under reduced pressure to give the title compound (0.005g) as a colourless gum.

Hplc system 1 (λ = 254nm) Rt 7.2min

Mass spectrum: Found: MH^+ 418 (^{35}Cl)

Example 27

3-Chloro-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-thiazol-2-yl-benzamide trifluoroacetate

To a stirred solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.050g), TBTU (0.074g) and HOBt (0.018g) in DMF (0.9ml) was added DIPEA (0.045ml) followed by N-propyl-2-amino-thiazole (0.037g) after 15min. The reaction mixture was stirred at room temperature for 20h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the product (0.022g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure. A solution of this product in trifluoroacetic acid (2ml) was stored at room temperature for 18h and the solvent removed under reduced pressure to give the title compound (0.019g) as a colourless gum.

Hplc system 1 (λ = 254nm) Rt 8.5min

Mass spectrum: Found: MH^+ 417 (^{35}Cl)

Example 28

3-Chloro-N-ethyl-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide hydrochloride

A solution {2-[3-chloro-5-(ethyl-phenyl-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.080g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 90min and then concentrated under reduced pressure. The residue was triturated with ethereal hydrogen chloride to give the title compound (0.068g) as a colourless solid.

Hplc system 1 (λ = 254nm) Rt 7.7min

Mass spectrum: Found: MH^+ 396.1483 $C_{22}H_{23}{}^{35}Cl_1N_3O_2$ requires 396.1479

Example 29

3-Chloro-N-(3,5-difluoro-phenyl)-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution (2-{3-chloro-5-[(propyl)-(3,5-difluoro-phenyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.029g) in trifluoroacetic acid (2ml) was stored at room temperature for 18h and then concentrated under reduced pressure.

The residue was subjected to preparative hplc and the title compound (0.020g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 9.0min

Mass spectrum: Found: MH^+ 446 (^{35}Cl)

Example 30

3-Chloro-N-ethyl-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

2M Oxalyl chloride solution in dichloromethane (0.080ml) and DMF (0.001ml) were added to a suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.050g) in anhydrous dichloromethane (1ml). The reaction was stirred at room temperature for 2h then a solution of N-ethyl-2-fluoroaniline (0.029g), DMAP (0.001g) and DIPEA (0.070ml) were added. The reaction mixture was stirred at room temperature for 16h and then triflouroacetic acid (1ml) was added. The solvent was removed *in vacuo*, the residue was subjected to preparative hplc and the required fraction dried by repetitive addition of acetonitrile and concentration under reduced pressure to give the title compound (0.020g) as a colourless gum.

Hplc system 1 (λ = 254nm) Rt 7.9min

Mass spectrum: Found: MH^+ 414 (^{35}Cl)

Example 31

N-(2-Carbamoyl-ethyl)-3-chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

2M Oxalyl chloride solution in dichloromethane (0.090ml) and DMF (0.001ml) were added to a suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.059g) in anhydrous dichloromethane (1ml). The reaction was stirred at room temperature for 2h then 3-phenylamino-propionitrile[8] (0.027g), DMAP (0.002g) and DIPEA (0.078ml) were added. The reaction mixture was stirred at room temperature for 2h then trifluoroacetic acid (2ml) was added and the reaction mixture stirred overnight open to the air. The reaction mixture was concentrated *in vacuo* and the residue was subjected to preparative hplc. The title compound (0.060g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 5.9min
Mass spectrum: Found: MH^+ 439.1528 $C_{23}H_{24}{}^{35}Cl_1N_4O_3$ requires 439.1537

Example 32

N-(2-Carbamoyl-ethyl)-3-chloro-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[(2-cyano-ethyl)-(2-fluoro-phenyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.055g) and water (0.020ml) in a mixture of trifluoroacetic acid (1ml) and dichloromethane (1ml) was stirred at room temperature for 2h and then the solvent removed under reduced pressure. The residue was purified by preparative hplc to give the title compound (0.035g) as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 1 (λ = 254nm) Rt 5.7min
Mass spectrum: Found: MH^+ 457.1435 $C_{23}H_{23}{}^{35}Cl_1F_1N_4O_3$ requires 457.1443

Example 33

N-(2-Carbamoyl-ethyl)-3-chloro-N-(2-chloro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[(2-chloro-phenyl)-(2-cyano-ethyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.055g) and water (0.020ml) in a mixture of trifluoroacetic acid (1ml) and dichloromethane (1ml) was stirred at room temperature for 2h and then the solvent removed under reduced pressure. The residue was purified by preparative hplc to give title compound (0.035g) as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 1 (λ = 254nm) Rt 6.0min
Mass spectrum: Found: MH^+ 473.1130 $C_{23}H_{23}{}^{35}Cl_2N_4O_3$ requires 473.1147

Example 34

4-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-phenyl)-amino]-butyric acid methyl ester trifluoroacetate

A solution of 4-[{3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-(2-fluoro-phenyl)-amino]-butyric acid methyl ester (0.020g) in a mixture of

dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 16h and then concentrated under reduced pressure to give the title compound (0.022g) as a colourless gum.
Hplc system 1 (λ = 254nm) Rt .8.1min
Mass spectrum: Found: MH^+ 486.1576 $C_{25}H_{26}{}^{35}Cl_1F_1N_3O_4$ requires 486.1596

Example 35

4-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-phenyl)-amino]-butyric acid

A solution of 4-[{3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-(2-fluoro-phenyl)-amino]-butyric acid (0.020g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 2h and then concentrated under reduced pressure to give the title compound (0.023g) as a colourless gum.
Hplc system 3 (λ = 220-330nm) Rt 3.1min
Mass spectrum: Found: MH^+ 472.1453 $C_{24}H_{24}{}^{35}Cl_1F_1N_3O_4$ requires 472.1439

Example 36

N-(3-Carbamoyl-propyl)-3-chloro-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-[(3-Carbamoyl-propyl)-(2-fluoro-phenyl)-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.030g) in trifluoroacetic acid (2ml) was stored at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.009g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 1 (λ = 254nm) Rt 6.0min
Mass spectrum: Found: MH^+ 471.1594 $C_{24}H_{25}{}^{35}Cl_1F_1N_4O_3$ requires 471.1599

Example 37

3-Chloro-N-(2-fluoro-phenyl)-N-(4-oxo-4-pyrrolidin-1-yl-butyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[(2-fluoro-phenyl)-(4-oxo-4-pyrrolidin-1-yl-butyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.025g) in mixture of trifluoroacetic acid (1ml) and dichloromethane (1ml) was stored at room

temperature for 1h and then the solvent removed under reduced pressure. The residue was subjected to preparative hplc to give the title compound (0.024g) as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 7.7min

Mass spectrum: Found: MH^+ 525.2063 $C_{28}H_{31}{}^{35}Cl_1F_1N_4O_3$ requires 525.2068

Example 38

4-{(2-Carbamoyl-phenyl)-[3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-amino)-butyric acid methyl ester trifluoroacetate

A solution of 4-[{3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-(2-carbamoyl-phenyl)-amino]-butyric acid methyl ester (0.031g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 1h and then concentrated under reduced pressure to give the title compound (0.032g) as a colourless gum.

Hplc system 1 (λ = 254nm) Rt .6.2min

Mass spectrum: Found: MH^+ 511

Example 39

4-{(2-Carbamoyl-phenyl)-[3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-amino)-butyric acid

2M Aqueous sodium hydroxide (0.200ml) was added to a stirred solution of 4-{(2-carbamoyl-phenyl)-[3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-amino)-butyric acid methyl ester trifluoroacetate (0.030g) in 1,4-dioxan (1ml). 2M Aqueous hydrochloric acid (0.2ml) was added after 16h.The reaction mixture was evaporated *in vacuo* and the residue was subjected to preparative hplc to give the title compound (0.024g) as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 2 (λ = 254) Rt 8.0min

Mass spectrum: Found: $(M-H_2O)H^+$ 479.1492 $C_{25}H_{24}{}^{35}Cl_1N_4O_4$ requires 479.1486

Example 40

3-Chloro-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[3-(1H-tetrazol-5-yl)-propyl]-benzamide

A mixture of (2-{3-chloro-5-[(3-cyano-propyl)-2-fluoro-phenyl)-carbamoyl}-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.132g) and tributyltin azide (1.2ml) was heated at 160°C for 5h. The reaction mixture was cooled to room temperature and 1M ethereal hydrogen chloride was added. The reaction mixure was partioned between acetonitrile and petroleum ether. The acetonitrile layer was removed and extracted further with petroleum ether. The acetonitrile layer was then subjected to prepartive hplc to give the title compound as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 6.6min

Mass spectrum: Found: MH^+ 496.1684 $C_{24}H_{24}{}^{35}Cl_1F_1N_7O_2$ requires 496.1664

Example 41

3-Chloro-N-[2-(2,3-dihydroxy-propoxy)-ethyl]-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of [2-{3-chloro-5-{[2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-ethyl]-phenyl-carbamoyl}-phenoxy)-ethyl]-pyridin-4-yl-carbamic acid tert-butyl ester (0.037g) in mixture of trifluoroacetic acid (1ml) and dichloromethane (1ml) was stored at room temperature for 3h and then the solvent removed under reduced pressure. The residue was subjected to preparative hplc to give the title compound (0.010g) as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 5.9min

Mass spectrum: Found: MH^+486 (^{35}Cl)

Example 42

3-Chloro-N-[2-(2,3-dihydroxy-propoxy)-ethyl]-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[[2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-ethyl}-(2-fluoro-phenyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.035g) and water (0.010ml) in mixture of trifluoroacetic acid (1ml) and dichloromethane (1ml) was stored at room temperature for 3h and then the solvent removed under reduced pressure. The residue was subjected to preparative hplc to give the title compound (0.022g) as a colourless gum by concentration of the

required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 5.8min

Mass spectrum: Found: MH^+ 504.1709 $C_{25}H_{28}{}^{35}Cl_1F_1N_3O_5$ requires 504.1701

Example 43

3-Chloro-N-[2-(2,3-dihydroxy-propoxy)-ethyl]-N-(4-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide hydrochloride

A solution of (2-{3-chloro-5-[[2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-ethyl]-(4-fluoro-phenyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.042g) in mixture of trifluoroacetic acid (1ml) and dichloromethane (1ml) was stored at room temperature for 3h and then the solvent removed under reduced pressure. The residue was dissolved in a mixture of acetonitrile (2ml) amd 2M aqueous hydrochloric acid (0.5ml) and subjected to preparative hplc to give title compound (0.022g) as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 5.8min

Mass spectrum: Found: MH^+ 504.1709 $C_{25}H_{28}{}^{35}Cl_1F_1N_3O_5$ requires 504.1701

Example 44

(R)-1-{3-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-phenyl)-amino]-propyl}-pyrrolidine-2-carboxylic acid trifluoroacetate

A solution of (R)-1-{3-[{3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-(2-fluoro-phenyl)-amino]-propyl}-pyrrolidine-2-carboxylic acid tert-butyl ester and (R)-1-[3-(2-fluoro-phenylamino)-propyl]-pyrrolidine-2-carboxylic acid tert butyl ester (0.110g) in trifluoroacetic acid (5ml) for 18h and then the solvent removed under reduced pressure. The residue was subjected to preparative hplc to give the titie compound (0.027g) as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 5.5min

Mass spectrum: Found: MH^+ 541.2000 $C_{28}H_{30}{}^{35}Cl_1F_1N_4O_4$ requires 541.2018

Example 45

3-Chloro-N-(3-oxo-3-piperidin-1-yl-propyl)-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

The following procedure was performed using a TECAN despensing robot. To a 0.1M solution of 3-({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-phenyl-amino)-propionic acid in DMF (0.250ml) was dispensed a 0.4M solution of PyBroP® in DMF (0.125ml) and a 0.2M solution of piperidine (0.375ml). Finally a 1M solution of DIPEA in DMF (0.100ml) was added to the reaction mixture. The reaction mixture was stored at room temperature for 24h, and then concentrated. The residue was stored in a mixture of dichloromethane (0.5ml) and trifluoroacetic acid (1ml) for 6h and concentrated. The residue was then subjected to preparative hplc and the title compound (0.008g) obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 3 (λ = 220-330nm) Rt 3.8min

Mass spectrum: Found: MH^+ 506 (^{35}Cl)

Using commercially available amines, the following compounds were prepared by the same method:

Example 46

3-Chloro-N-[2-(ethyl-methyl-carbamoyl)-ethyl]-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 3 (λ = 220-330nm) Rt 3.6min

Mass spectrum: Found: MH^+ 481 (^{35}Cl)

Example 47

N-(2-tert-Butylcarbamoyl-ethyl)-3-chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 3 (λ = 220-330nm) Rt 3.7min

Mass spectrum: Found: MH^+ 495 (^{35}Cl)

Example 48

3-Chloro-N-[2-(2,2-dimethyl-propylcarbamoyl)-ethyl]-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 3 (λ = 220-330nm) Rt 3.8min

Mass spectrum: Found: MH^+ 509 (^{35}Cl)

Example 49

3-Chloro-N-(3-oxo-3-thiomorpholin-4-yl-propyl)-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 3 (λ = 220-330nm) Rt 3.7min

Mass spectrum: Found: MH^+ 525 (^{35}Cl)

Example 50

3-Chloro-N-(3-oxo-3-thiazolidin-3-yl-propyl)-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 3 (λ = 220-330nm) Rt 3.6min

Mass spectrum: Found: MH^+ 511 (^{35}Cl)

Example 51

3-Chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-sulfamoyl-ethyl)-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[(2-fluorosulfonyl-ethyl)-phenyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.017g) in a mixture of acetone (10ml) and ammonia(0.88) was stirred at 80°C for 3h. The solvent was removed under reduced pressure and the residue subjected to preparative hplc. A solution of this product in a mixture of trifluoroacetic acid (3ml) and dichloromethane (1.5ml) was stored for 1h then evaporated to give the title compound as a colourless gum (0.009g).

Hplc system 1 (λ = 254nm) Rt 6.4min

Mass spectrum: Found: MH^+ 475.1214 $C_{22}H_{24}{}^{35}Cl_1N_4O_4S_1$ requires 475.1207

Example 52

N-(2-tert-Butylsulfamoyl-ethyl)-3-chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[(2-fluorosulfonyl-ethyl)-phenyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.020g) in tert-butylamine (0.75ml) was stored at room temperature for 24h. The amine was evaporated and the residue dissolved in a mixture of trifluoroacetic acid (1ml) and dichloromethane (0.5ml) and was stored for 64h. The solvent was removed and the residue subjected to preparative hplc. The title compound (0.015g) was obtained as a yellow

gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 7.8min

Mass spectrum: Found: MH^+ 531 (^{35}Cl)

Example 53

3-Chloro-N-(2-isopropylsulfamoyl-ethyl)-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[(2-fluorosulfonyl-ethyl)-phenyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.020g) in isopropylamine (0.75ml) was stored at room temperature for 24h. The amine was evaporated *in vacuo* and the residue dissolved in a mixture of trifluoroacetic acid (1ml) and dichloromethane (0.5ml) was stored for 64h. The solvent was removed and the residue subjected to preparative hplc. The title compound (0.015g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 7.8min

Mass spectrum: Found: MH^+ 517 (^{35}Cl)

Example 54

3-Chloro-N-isopropyl-N-[2-(1-methyl-1H-tetrazol-5-yl)-ethyl]-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of {2-(3-chloro-5-{isopropyl-[2-(1-methyl-1H-tetrazol-5-yl)-ethyl]-carbamoyl}-phenoxy)-ethyl]-pyridin-4-yl-carbamic acid tert-butyl ester (0.028g) in a mixture of dichloromethane (0.5ml) and trifluoroacetic acid (1ml) was stored at room temperature for 2h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.023g) was obtained as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 6.1min

Mass spectrum: Found: MH^+ 444.1913 $C_{21}H_{27}{}^{35}Cl_1N_7O_2$ requires 444.1915

Example 55

N-(2-Carbamoyl-ethyl)-3-chloro-N-cyclopropylmethyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[(2-cyano-ethyl)-cyclopropylmethyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.07g) in a mixture of dichloromethane (5ml) and trifluoroacetic acid (2ml) was stored at room temperature for 18h and then concentrated under reduced pressure to give the title compound as a light brown oil (0.071g).

Hplc system 1 (λ = 254nm) Rt 5.8min

Mass spectrum: Found: MH^+ 417.1709 $C_{21}H_{26}{}^{35}ClN_4O_3$ requires 417.1693

Example 56

N-(2-Carbamoyl-ethyl)-3-chloro-N-(2,2-dimethyl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[(2-cyano-ethyl)-(2,2-dimethyl-propyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.052g) in a mixture of dichloromethane (5ml) and trifluoroacetic acid (2ml) was stored at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.02g) was obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 6.4min

Mass spectrum: Found: MH^+ 433.1995 $C_{22}H_{30}{}^{35}ClN_4O_3$ requires 433.2006

Example 57

N-(2-Carbamoyl-ethyl)-3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(tetrahydro-furan-2-ylmethyl)-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[(2-cyano-ethyl)-(tetrahydro-furan-2-ylmethyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.052g) in a mixture of dichloromethane (5ml) and trifluoroacetic acid (2ml) was stored at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.037g) was obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 5.3min

Mass spectrum: Found: MH^+ 447.1807 $C_{22}H_{28}{}^{35}ClN_4O_4$ requires 447.1799

Example 58

N-(2-Carbamoyl-ethyl)-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[(2-cyano-ethyl)-isopropyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.071g) in a mixture of dichloromethane (4ml) and trifluoroacetic acid (1ml) was stored at room temperature for 12h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.045g) was obtained as a yellow oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 5.1min

Mass spectrum: Found: MH^+ 405 (^{35}Cl)

Example 59

N-(2-Carbamoyl-ethyl)-3-chloro-N-isobutyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[(2-cyano-ethyl)-isobutyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.059g) in a mixture of dichloromethane (5ml) and trifluoroacetic acid (2ml) was stored at room temperature for 18h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.047g) was obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 5.7min

Mass spectrum: Found: MH^+ 419 (^{35}Cl)

Example 60

3-Chloro-N-(2-diethylcarbamoyl-ethyl)-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[(2-diethylcarbamoyl-ethyl)-isopropyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester trifluoroacetate (0.06g) in a mixture of dichloromethane (2ml) and trifluoroacetic acid (1ml) was stored at room temperature for 3h and then concentrated under reduced pressure to give the title compound as a colourless oil (0.043g).

Hplc system 1 (λ = 254nm) Rt 7.6min

Mass spectrum: Found: MH^+ 461 (^{35}Cl)

Example 61

3-Chloro-N-isopropyl-N-(3-oxo-3-piperidin-1-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

To a stirred solution of 3-({3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-isopropyl-amino)-propionic acid hydrochloride (0.02g) and PyBroP® (0.035g) in DMF (0.45ml) was added DIPEA (0.026ml) followed by piperidine (0.014ml) after 5min. The reaction was stirred at room temperature for 24h, and then concentrated under reduced pressure. The remaining solid residue was stored in a mixture of dichloromethane (2ml) and trifluoroacetic acid (1ml) for 6h, and then concentrated under reduced pressure. The residue was then subjected to preparative hplc and the title compound (0.011g) obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 3 (λ = 220-330nm) Rt 3.65min

Mass spectrum: Found: MH^+ 473 (^{35}Cl)

Using commercially available amines, the following compounds were prepared in a similar manner:

Example 62

3-Chloro-N-[2-(3-methyl-but-2-yl-carbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 1 (λ =254nm) Rt 8.0 min

Mass spectrum: Found: MH^+ 475 (^{35}Cl)

Example 63

3-Chloro-N-[2-(3,3-dimethyl-but-2-yl-carbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 1 (λ = 254nm) Rt 8.5 min

Mass spectrum: Found: MH^+ 489 (^{35}Cl)

Example 64

3-Chloro-N-[2-(ethyl-methyl-carbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 3 (λ = 220-330nm) Rt 3.5min; Mass spectrum: Found: MH^+ 447 (^{35}Cl)

Example 65

3-Chloro-N-isopropyl-N-(3-oxo-3-pyrrolidin-1-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 3 (λ = 220-330nm) Rt 3.5min; Mass spectrum: Found: MH^+ 459 (^{35}Cl)

Example 66

3-Chloro-N-isopropyl-N-(3-morpholin-4-yl-3-oxo-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide mixture with 3-({3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isopropyl-amino)-propionic acid (1:2) trifluoroacetate

Hplc system 3 (λ = 220-330nm) Rt 3.4min; Mass spectrum: Found: MH^+ 475 (^{35}Cl)

Example 67

N-(2-tert-Butylcarbamoyl-ethyl)-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 3 (λ = 220-330nm) Rt 3.7min; Mass spectrum: Found: MH^+ 461 (^{35}Cl)

Example 68

3-Chloro-N-[2-(2,2-dimethyl-propylcarbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 3 (λ = 220-330nm) Rt 3.7min; Mass spectrum: Found: MH^+ 475 (^{35}Cl)

Example 69

3-Chloro-N-isopropyl-N-(3-oxo-3-thiomorpholin-4-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 3 (λ = 220-330nm) Rt 3.6min; Mass spectrum: Found: MH^+ 491 (^{35}Cl)

Example 70

3-Chloro-N-isopropyl-N-(3-oxo-3-thiazolidin-3-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 3 (λ = 220-330nm) Rt 3.6min; Mass spectrum: Found: MH^+ 477 (^{35}Cl)

Example 71

3-Chloro-N-[2-(1,1-dimethyl-propylcarbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 1 (λ = 254nm) Rt 8.4min

Mass spectrum: Found: MH^+ 475

Example 72

3-Chloro-N-isopropyl-N-(3-methanesulfonylamino-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

To a solution of N-(3-amino-propyl)-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate (0.02g) in dry acetonitrile (1ml) was added a mixture of methanesulfonyl chloride (0.005g) and triethylamine (0.017ml) in acetonitrile (1ml). The resultant mixture was stirred at room temperature for 15h, and then concentrated under reduced pressure. The residue was stored in a mixture of dichloromethane (1ml) and trifluoroacetic acid (2ml) for 4h, and then concentrated under reduced pressure. The residue was then subjected to preparative hplc and the title compound obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 6.5min

Mass spectrum: Found: MH^+ 469 (^{35}Cl)

Using commercially available sulfonyl chlorides, the following compounds were prepared in a similar manner:-

Example 73

3-Chloro-N-isopropyl-N-[3-(propane-1-sulfonylamino)-propyl]-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 1 (λ = 254nm) Rt 8.0min; Mass spectrum: Found: MH^+ 497 (^{35}Cl)

Example 74

3-Chloro-N-(3-ethanesulfonylamino-propyl)-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 1 (λ = 254nm) Rt 6.7min; Mass spectrum: Found: MH^+ 483 (^{35}Cl)

Example 75

3-Chloro-N-isopropyl-N-[3-(propane-2-sulfonylamino)-propyl]-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 1 (λ = 254nm) Rt 8.9min; Mass spectrum: Found: MH^+ 497 (^{35}Cl)

Example 76

1-{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-piperidine-2-carboxylic acid trifluoroacetate

1-{3-[2-(tert-Butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoyl}-piperidine-2-carboxylic acid ethyl ester (0.16g) in 1,4-dioxan (2ml) was treated with 2M sodium hydroxide solution (0.6ml) and stored at room temperature for 18h. The solution was concentrated under reduced pressure and the residue stored in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml). After 3h, the solution was concentrated under reduced pressure and the residue was subjected to preparative hplc. The title compound (0.100g) was obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 7.6min

Mass spectrum: Found: MH^+ 404 (^{35}Cl)

Example 77

{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-(2-methyl-piperidin-1-yl)-methanone trifluoroacetate

A solution of {2-[3-chloro-5-(2-methyl-piperidine-1-carbonyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.065g) in a mixture of dichloromethane (5ml) and trifluoroacetic acid (2ml) was stored at room temperature for 5h and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.061g) was obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 8.1min

Mass spectrum: Found: MH^+ 374 (^{35}Cl)

Example 78

3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-trifluoromethanesulfonylamino-propyl)-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[cyclopentyl-(3-trifluoromethanesulfonylamino-propyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.0118g) in dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 19h and then concentrated under reduced pressure. The title compound was obtained as a pale brown gum (0.010g).

Hplc system 1 (λ = 254nm) Rt 10.2min

Mass spectrum: Found: MH^+ 549.1567 $C_{23}H_{29}{}^{35}ClF_3N_4O_4S$ requires 549.1550

Example 79

3-Chloro-N-isopropyl-N-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of {2-[3-chloro-5-(isopropyl-methyl-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.060g) in dichloromethane (4ml) and trifluoroacetic acid (4ml) was stored at room temperature for 2h and then concentrated under reduced pressure. The residue was subjected to preparative hplc to give the title compound as a yellow gum (0.061g).

Hplc system 1 (λ = 254nm) Rt 6.8min

Mass spectrum: Found: MH^+ 348.1470 $C_{18}H_{23}{}^{35}ClN_3O_2$ requires 348.1479

Example 80

N-[2-(3-Amino-[1,2,4]oxadiazol-5-yl)-ethyl]-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of [2-(3-{[2-(3-amino-[1,2,4]oxadiazol-5-yl)-ethyl]-isopropyl-carbamoyl}-5-chloro-phenoxy)-ethyl]-pyridin-4-yl-carbamic acid tert-butyl ester (0.064g) in dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 5h and then concentrated under reduced pressure. The residue was subjected to preparative hplc to give the title compound as a pale yellow foam (0.043g).

Hplc system 1 (λ = 254nm) Rt 6.2min

Mass spectrum: Found: MH^+ 445.1743 $C_{21}H_{26}{}^{35}ClN_6O_3$ requires 445.1755

Example 81

N-(2-Cyano-ethyl)-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of 3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoic acid trifluoroacetate salt (0.026g) in anhydrous DMF (2ml) was treated at room temperature with 3-isopropylamino-propionitrile[9] (0.017g), PyBrop[©] (0.062g) and DIPEA (0.025ml). More PyBrop[©] was added after 2 days (0.072g) and 7 days (0.065g). More 3-isopropylamino-propionitrile was added after 2 days (0.03ml), 4 days (0.1ml) and 7 days (0.1ml). After 24h more, the mixture was evaporated to dryness under reduced pressure and the residue subjected to preparative hplc giving the title compound as a clear colourless gum (0.016g).

Hplc system 2 (λ = 254nm) Rt 9.6min

Mass spectrum: Found: MH^+ 367.2140 $C_{21}H_{27}N_4O_2$ requires 367.2134

Example 82

N-(2-Carbamoyl-ethyl)-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of N-(2-cyano-ethyl)-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate (0.011g) in dichloromethane (1.5ml) and trifluoroacetic acid (0.5ml) was stored at room temperature overnight and then concentrated under reduced pressure. The title compound was obtained as a pale yellow foam (0.012g).

Hplc system 2 (λ = 254nm) Rt 8.2min

Mass spectrum: Found: MH^+ 385

Example 83

3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)]-N-(2-[1,2,4]triazol-1-yl-ethyl)-benzamide

Tributyltin azide (1.0g) was added to (2-{3-chloro-5-[(2-cyano-ethyl)-cyclopentyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.11g). The neat mixture was heated at 160°C for 4h, cooled to room temperature and quenched with 2M sodium hydroxide solution and extracted with ether. The aqueous layer was acidified with 5M hydrochloric acid and subjected to preparative hplc to give the title compound (0.022g) as a colourless oil.

Hplc system 1 (λ = 254nm) Rt 6.5min

Mass spectrum: Found: MH^+ 456 (^{35}Cl).

Example 84

3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-[1,2,4]triazol-1-yl-ethyl)-benzamide trifluoroacetate

To a solution of (2-{3-chloro-5-[isopropyl-(2-[1,2,4]triazol-1-yl-ethyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.097g) in dichloromethane (5ml) was added trifluoroacetic acid (2ml) and the mixture was stirred at room temperature for 3h. The solvent was evaporated under reduced pressure and the residue subjected to preparative hplc to give the title compound (0.093g) as a clear oil.

Hplc system 1 (λ = 254nm) Rt 6.0min.

Mass spectrum: Found: MH^+ 544 (^{35}Cl).

Example 85

N-(3-Amino-propyl)-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide bis(trifluoroacetate)

A solution of (2-{3-[(3-amino-propyl)-isopropyl-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.025g) in dichloromethane (1ml) was treated with dichloromethane:trifluoroacetic acid (1:1 v/v) (1ml),stirred for 3h at room temperature and concentrated under reduced pressure. The residue was subjected to preparative hplc to give the title compound (0.018g) as a light brown oil.

Hplc system 1 (λ= 254nm) Rt 4.9min

Mass spectrum: Found: MH^+ 377 (^{35}Cl)

Example 86

3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-trifluoromethanesulfonylamino-propyl)-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[isopropyl-(3-trifluoromethanesulfonylamino-propyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester trifluoroacetate (0.038g) in dichloromethane (1ml) was treated with dichloromethane:trifluoroacetic acid (1:1 v/v) (1ml) stirred for 3h at room temperature and concentrated under reduced pressure. The residue was subjected to preparative hplc to give the title compound (0.024g) as an oil.

Hplc system 1 (λ= 254nm) Rt 8.9min

Mass spectrum: Found: MH^+ 523 (^{35}Cl)

Example 87

{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-(2,5-dimethyl-pyrrolidin-1-yl)-methanone trifluoroacetate

A solution of (2-{3-chloro-5-(2,5-dimethyl-pyrrolidine-1-carbonyl)-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.260g) in dichloromethane (1ml) was treated with dichloromethane:trifluoroacetic acid (1:1 v/v) (1ml), stirred for 3h at room temperature and concentrated under reduced pressure. The residue was taken up into ethyl acetate and filtered through silica (50g) to give the title compound (0.102g) as an oil.

Hplc system 1 (λ= 254nm) Rt 7.5min

Mass spectrum: Found: MH^+ 374 (^{35}Cl)

Example 88

3-Chloro-N-[3-(2,2-dimethyl- propionylamino)-propyl]-N- isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]- benzamide trifluoroacetate

A solution of [2-(3-chloro-5-{[3-(2,2-dimethyl-propionylamino)-propyl]-isopropyl-carbamoyl}-phenoxy)-ethyl]-pyridine-4-yl-carbamic acid tert-butyl ester in dichloromethane (1ml) was treated with dichloromethane:trifluoroacetic acid (1:1 v/v) (1ml), stirred for 3h at room temperature and concentrated under reduced pressure. The residue was subjected to preparative hplc to give the title compound (0.039g) as an oil.

Hplc system 3 (λ=220-330nm) Rt 3.7min

Mass spectrum: Found: MH^+ 475 (^{35}Cl)

Example 89

3-Chloro-N-[3-(2,2-dimethyl-propionylamino)-propyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

To a solution of (2-{3-[(3-amino-propyl)-isopropyl-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.040g), DIPEA (0.03ml) in dichloromethane (1ml) was added a solution of tert-butyl acetyl chloride (0.014ml) in dichloromethane (1ml) and the mixture was stirred for 3h at room temperature. The mixture was evaporated under reduced pressure, was dissolved in dichloromethane (1ml), was treated with 1ml of dichloromethane:trifluoroacetic acid (1:1), stirred for 3h at room temperature and concentrated under reduced pressure. The residue was subjected to preparative hplc to give the title compound (0.037g) as an oil.

Hplc system 3 (λ=220-330nm) Rt 2.7min

Mass spectrum: Found MH^+ 489 (^{35}Cl)

Example 90

3-Chloro-N-(4-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-[1,2,4]triazol-1-yl-propyl)-benzamide bis(trifluoroacetate)

A suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.050g), 4-fluorophenyl-(3-[1,2,4]triazol-1-yl-propyl)-amine (0.056g) and EEDQ (0.050g) in acetonitrile (1ml) was stirred at 50°C under nitrogen for 5h. The solvent was removed and the residue was purified by flash chromatography on silica eluting with dichloromethane:methanol:ammonia (99:1:0.1 v/v/v). The resultant oil was treated with trifluoroacetic acid then concentrated under vacuum to give the title compound as a colourless gum (0.008g).

Hplc system 3 (λ=220-330nm) Rt 3.7min

Mass spectrum: Found: MH^+ 495 (^{35}Cl)

Example 91

3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-[1,2,4]triazol-1-yl-ethyl)-benzamide

A solution of 2-[3-chloro-5-(cyclopentyl-(2-[1,2,4]triazol-1-yl-ethyl)-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.022g) and trifluoroacetic acid (0.5ml) in dicloromethane (0.5ml) was stirred at room temperature for 1h then concentrated under vacuum. The residue was purified by flash chromatography eluting with dichloromethane:methanol (90:10 then 80:20 v/v) to give the title compound as an off-white powder (0.013g).

Mass spectrum: Found: MH^+ 455 (^{35}Cl)

Hplc system 1 (λ = 254nm) Rt 7.0min

Example 92

3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(4-[1,2,4]triazol-1-yl-butyl)-benzamide

A solution of {2-[3-chloro-5-(cyclopentyl-(4-[1,2,4]triazol-1-yl-butyl)-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.069g) and trifluoroacetic acid (0.5ml) in dichloromethane (0.5ml) was stirred at room temperature for 1h then concentrated under vacuum. The residue was purified by flash chromatography eluting with dichloromethane:methanol:ammonia (92:8:1 v/v/v), to give the title compound as a white foam (0.026g).

Mass spectrum: Found: MH^+ 483 (^{35}Cl)

Hplc system 1 (λ = 254nm) Rt 6.9min

Example 93

3-Chloro-N-(4-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-tetrazol-2-yl-propyl)-benzamide trifluoroacetate

A suspension of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.05g) 4-fluorophenyl-(3-tetrazol-2-yl-propyl)-amine (0.056g) and EEDQ (0.05g) in acetonitrile (1ml) was stirred under nitrogen at room temperature for 18h then at 50°C for 2h. The solvent was removed and the residue was purified by flash chromatography, eluting with dichloromethane:methanol:ammonia (99:1:0.1 v/v/v). The resultant oil was treated with trifluoroacetic acid then concentrated under vacuum to give the title compound as a colourless gum (0.004g).

Mass spectrum: Found: MH^+ 496 (^{35}Cl)

Hplc system 3 (λ =220-330nm) Rt 3.6min

Example 94

3-Chloro-N-(3-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-tetrazol-2-yl-propyl)-benzamide

A solution of {2-[3-chloro-5-(3-fluorophenyl-(3-tetrazol-2-yl-propyl)-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.07g) in trifluoroacetic acid (0.75ml) and dichloromethane (0.75ml) was stirred at room temperature for 1h then concentrated under vacuum. The residue was purified by flash chromatography, eluting with dichloromethane/methanol/ammonia (90:10:1) to give the title compound as a white foam (0.042g).

Mass spectrum: Found: MH^+ 496 (^{35}Cl)

Hplc system 3 (λ = 220-330nm) Rt 3.5min

Example 95

3-Chloro-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-tetrazol-2-yl-propyl)-benzamide

A solution of {2-[3-chloro-5-(2-fluorophenyl-(3-tetrazol-2-yl-propyl)-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.048g) in trifluoroacetic acid (0.5ml) and dichloromethane (0.5ml) was stirred at room temperature for 1h then concentrated under vacuum. The residue was purified by flash chromatography, eluting with dichloromethane:methanol:ammonia (95:5:0.5 then 90:10:1 v/v/v), to give the title compound as an off-white foam (0.035g).

Mass spectrum: Found: MH^+ 496 (^{35}Cl)
Hplc system 3 (λ = 220-330nm) Rt 3.5min

Example 96

3-Chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-tetrazol-2-yl-ethyl)-benzamide trifluoroacetate

A solution of {2-[3-chloro-5-(phenyl-(3-tetrazol-2-yl-propyl)-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.024g) in trifluoroacetic acid (0.25ml) and dichloromethane (0.25ml) was stirred at room temperature for 2h then concentrated under vacuum, co-evaporating with dichloromethane to give the title compound as an off-white foam (0.026g).
Mass spectrum: Found: MH^+ 464 (^{35}Cl)
Hplc system 3 (λ = 220-330nm) Rt 3.5min

Example 97

3-Chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-[1,2,3]triazol-2-yl-ethyl)-benzamide trifluoroacetate

A solution of {2-[3-chloro-5-(phenyl-(3-[1,2,3]-triazol-2-yl-propyl)-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.083g) and trifluoroacetic acid (1ml) in dichloromethane (1ml) was stirred at room temperature for 2h then concentrated under vacuum, co-evaporating with dichloromethane to give the title compound as a yellow-brown oil (0.103g).
Mass spectrum: Found: MH^+ 463 (^{35}Cl)
Hplc system 3 (λ = 220-330nm) Rt 3.6min

Example 98

3-Chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[2-(pyridin-2-yloxy)-ethyl]-benzamide bis(trifluoroacetate)

A solution of {2-[3-chloro-5-(phenyl-2-(pyridin-2-yloxy)-ethyl-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.065g) and trifluoroacetic acid (0.75ml) in dichloromethane (0.75ml) was stirred at room temperature for 2h then concentrated under vacuum, co-evaporating with dichloromethane to give the title compound as a yellow oil (0.086g).
Mass spectrum: Found: MH^+ 489 (^{35}Cl)
Hplc system 3 (λ = 220-330nm) Rt 3.8min

Example 99

3-Chloro-N-isopropyl-N-(2-methoxy-ethyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide

A solution of {2-[3-chloro-5-(isopropyl-2-methoxy-ethyl-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (Intermediate SS8) (0.056g) and trifluoroacetic acid (0.6ml) in dichloromethane (0.6ml) was stirred at room temperature for 1h then concentrated under vacuum. The residue was purified by flash chromatography eluting with dichloromethane:methanol:ammonia (94:6:1 then 92:8:1 v/v/v), to give the title compound as a colourless gum (0.036g).
Mass spectrum: Found: MH^+ 392 (^{35}Cl)
Hplc System 3 (λ = 220-330nm) Rt 3.5min

Example100

3-(Isopropyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-amino)-propionic acid methyl ester trifluoroacetate

To a stirred solution of 3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoic acid trifluoroacetate (0.025g) and TBTU (0.021g) in DMF (1ml) was added DIPEA (0.022ml) followed by 3-isopropylamino-propionic acid methyl ester (0.01g) after 3 min. The reaction was stirred at room temperature for 18h, and then concentrated under reduced pressure. The residue was subjected to preparative hplc to give the title compound (0.031g) as a colourless oil, by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 1 (λ = 254nm) Rt 6.8min
^{1}H-NMR (CD_3OD, 250 MHz) δ 8.15 (d,1H). 7.98 (d,1H), 7.05 (m,1H), 6.9 (m,2H), 6.75 (m,2H), 4.21 (t,2H), 3.95 (m,1H), 3.55-3.80 (m,7H), 2.65 (t,2H), 2.35 (s,3H), 1.15 (d,6H)

Example 101

3-(Isopropyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-amino)-propionic acid trifluoroacetate

To a solution of 3-(isopropyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-amino)-propionic acid methyl ester trifluoroacetate (0.031g) in dioxan (1ml) was added 2M aqueous sodium hydroxide (0.078ml), and the resultant solution was stirred at room temperature for 3h. 1M Aqueous hydrochloric acid (*ca* 0.5ml) was added and the resultant solution was concentrated under reduced pressure. Th

residue was subjected to preparative hplc and the title compound (0.027g) was obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Mass spectrum: Found: MH^+ 386

hplc system 1 (λ=254nm) Rt 5.5min

Example 102

6-{[3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl]-isopropyl-amino}-hexanoic acid trifluoroacetate

P-Benzyloxybenzylalcohol (Wang) resin[10] (0.54mmol/g, 0.250g) was wetted with DMF (*ca.* 2ml) and then treated with a mixture of 6-bromohexanoic acid (0.173g), diisopropylcarbodiimide (0.139ml) and 4-dimethylaminopyridine (2mg) in dry DMF (1ml). The mixture was agitated for 5 days and then filtered dry under suction. The resin was repeatedly washed with DMF (x3), and dichloromethane (x3) before drying under suction. The resin was then agitated with isopropylamine (1.5ml) in dry DMF (1.5ml) for 2 days. After filtration, the resin was repeatedly washed with DMF (x3) and dichloromethane (x3). The resin was then agitated with 3-methyl-5-[2-(pyridin-4ylamino)-ethoxy]-benzoic acid (0.16g), diisopropylcarbodiimide (0.127ml) and 4-dimethylaminopyridine (0.012g) for 3 days. After the excess reagents were removed by filtration, the resin was washed with DMF (x3) and dichloromethane (x3) before treatment with dichloromethane (1ml) and trifluoroacetic acid (1ml). After 1.5h, the resin was filtered and washed thoroughly with dichloromethane. The combined filtrate and washings were evaporated to dryness under reduced pressure and subjected to preparative hplc. Evaporation of the required fraction gave the title compound as a gum (0.048g).

Hplc system 1 (λ = 254nm) Rt 6.7min

[10]p-Benzyloxybenzyl alcohol resin - polymer matrix is copoly(styrene-1% divinylbenzene), 100-200 mesh; Novabiochem cat. no. 01-64-0014

Mass Spectrum: Found: MH^+ 428

Example 103

N-tert-Butyl-N-(2-tert-butylcarbamoyl-ethyl)-3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A suspension of 5% Pd on carbon (0.020g) in a solution of (2-{3-[tert-butyl-(2-tert-butylcarbamoyl-ethyl)-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic

acid benzyl ester (0.024g) in 1,4-dioxan (5ml) was stirred under an atmosphere of hydrogen for 20h. The catalyst was removed by filtration and the filtrate evaporated *in vacuo*. The residue was subjected to preparative hplc to give the title compound (0.003g) as a colourless gum.

Hplc system 1 (λ = 254nm) Rt 8.2min

Mass spectrum: Found: MH^+ 475.2478 $C_{25}H_{36}{}^{35}Cl_1N_4O_3$ requires 475.2476

Example 104

N-(2-tert-Butylcarbamoyl-ethyl)-3-chloro-N-cyclobutyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-[(2-tert-butylcarbamoyl-ethyl)-cyclobutyl-carbamoyl]-5-chloro-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.021g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 64h and then concentrated under reduced pressure to give the title compound (0.020g) as a colourless gum.

Hplc system 1 (λ = 254nm) Rt 7.6min

Mass spectrum: Found: MH^+ 473.2332 $C_{25}H_{34}{}^{35}Cl_1N_4O_3$ requires 473.2319

Example 105

3-Chloro-N-cyclobutyl-N-[2-(2,2-dimethyl-propylcarbamoyl)-ethyl]-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of [2-(3-chloro-5-{cyclobutyl-[2-(2,2-dimethyl-propylcarbamoyl)-ethyl]-carbamoyl}-phenoxy)-ethyl]-pyridin-4-yl-carbamic acid tert-butyl ester (0.016g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 64h and then concentrated under reduced pressure to give the title compound (0.012g) as a colourless gum.

Hplc system 1 (λ = 254nm) Rt 8.1min

Mass spectrum: Found: MH^+ 487.2462 $C_{26}H_{36}{}^{35}Cl_1N_4O_3$ requires 487.2476

Example 106

N-(2-Carbamoyl-ethyl)-3-chloro-N-cyclobutyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

A solution of (2-{3-chloro-5-[(2-cyano-ethyl)-cyclobutyl-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.042g) and water (0.050ml) in mixture of trifluoroacetic acid (1ml) and dichloromethane (1ml) was stored at room temperature for 24h and then the solvent removed under reduced pressure. The residue was

subjected to preparative hplc to give the title compound (0.027g) as a colourless gum by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 1 (λ = 254nm) Rt 5.6min
Mass spectrum: Found: MH^+ 417

Example 107
3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-sulfamoyl-ethyl)-benzamide trifluoroacetate
A solution of (2-{3-chloro-5-[isopropyl-(2-sulfamoyl-ethyl)-carbamoyl]-phenoxy}-ethyl)-pyridin-4-yl-carbamic acid tert-butyl ester (0.012g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 64h and then concentrated under reduced pressure to give the title compound (0.011g) as a colourless gum.
Hplc system 1 (λ = 254nm) Rt 5.6min
Mass spectrum: Found: MH^+ 441

Example 108
3-Chloro-N-(2,2-dimethyl-propylsulfamoyl-ethyl)-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate
A solution of [2-(3-chloro-5-{[2-(2,2-dimethyl-propylsulfamoyl)-ethyl]-isopropyl-carbamoyl}-phenoxy)-ethyl]-pyridin-4-yl-carbamic acid tert-butyl ester (0.042g) in a mixture of dichloromethane (1ml) and trifluoroacetic acid (1ml) was stored at room temperature for 64h and then concentrated under reduced pressure to give the title compound (0.024g) as a straw coloured gum.
Hplc system 1 (λ = 254nm) Rt 8.7min
Mass spectrum: Found: MH^+ 511.2143 $C_{22}H_{35}{}^{35}Cl_1N_4O_4S_1$ requires 511.2146

Example 109
3-Chloro-N-[2-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-ethyl]-N-isopropyl-5-[2[(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate
A solution of (3-chloro-N-[2-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-ethyl]-N-isopropyl-5-[2[(pyridin-4-ylamino)-ethoxy]-benzamide carbamic acid tert-butyl ester (0.046g) in a mixture of DCM (3ml) and trifluoroacetic acid (1ml) was stirred at room temperature for 3h. The solvent was evaporated under pressure and the residue subjected to preparative hplc to give the title compound (0.027g) as a clear oil.

Mass spectrum: Found: MH^+ 446 (^{35}Cl).
Hplc system 1 (λ = 254nm) Rt 6.16min.

Example 110
N-(2-tert-Butylcarbamoyl-ethyl)-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate
To a stirred solution of 3-(isopropyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-amino)-propionic acid trifluoroacetate (0.018g) and PyBroP® (0.017g) in DMF (1ml) was added DIPEA (0.012ml) followed by tert-butylamine (0.005ml), after 1min. The reaction mixture was stirred at room temperature for 18h, and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.009g) was obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 3 (λ = 220-330nm) Rt 3.8min
Mass spectrum: Found: MH^+ 441

Similarly prepared was:

Example 111
N-[2-(2,2-dimethylpropylcarbamoyl)-ethyl]-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide
Hplc system 3 (λ = 220-330nm) Rt 4.1min
Mass spectrum: Found: MH^+ 455

Example 112
N-(5-tert-Butylcarbamoyl-pentyl)-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate
To a stirred solution of 6-({3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isopropyl-amino)-hexanoic acid trifluoroacetate (0.02g) and PyBroP® (0.021g) in DMF (1ml) was added DIPEA (0.016ml) followed by tert-butylamine (0.005ml), after 1min. The reaction mixture was stirred at room temperature for 18h, and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.0094g) was obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.

Hplc system 1 (λ = 254nm) Rt 8.3min
Mass spectrum: Found: MH$^+$ 503

Similarly prepared was:

Example 113
3-Chloro-N-[5-(2,2-dimethyl-propylcarbamoyl)-pentyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate
Hplc system 1 (λ = 254nm) Rt 8.7min
Mass spectrum: Found: MH$^+$ 517

Example 114
N-[5-tert-Butylcarbamoyl)-pentyl]-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate)
To a stirred solution of 6-[{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(isopropyl) -amino]-hexanoic acid trifluoroacetate (0.026g) and PyBroP® (0.022g) in DMF (1ml) was added DIPEA (0.018ml) followed by tert-butylamine (0.005ml), after 1min. The reaction mixture was stirred at room temperature for 18h, and then concentrated under reduced pressure. The residue was subjected to preparative hplc and the title compound (0.002g) was obtained as a colourless oil by concentration of the required fraction under reduced pressure and drying by repetitive addition of acetonitrile and concentration under reduced pressure.
Hplc system 1 (λ = 254nm) Rt 8.2min
Mass spectrum: Found: MH$^+$ 483

Example 115
N-(5-Carbamoyl-pentyl)-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate
To a solution of 6-[{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(isopropyl) -amino]-hexanoic acid trifluoroacetate (0.022g) in DMF (1ml) was added HATU® (0.039g), DIPEA (0.018ml) and 0.5M ammonia in 1,4-dioxane solution (0.2ml). The mixture was stirred overnight. The reaction mixture was evaporated under reduced pressure, the residue obtained was subjected to preparative hplc to give the title compound as a colourless oil(0.008g)
Hplc system 1 (λ= 254nm) Rt 5.9 min
Mass spectrum: Found: MH$^+$ 427

Example 116
3-Chloro-N-(2-(4-tert-butylphenyl)-ethyl)-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide
A solution of {2-[3-chloro-5-(isopropyl-(2-(4-tert-butylphenyl)-ethyl-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.062g) in trifluoroacetic acid (0.75ml) and dichloromethane (0.75ml) was stirred at room temperature for 1h then concentrated under vacuum. The residue was purified by flash chromatograpy, eluting with dichloromethane:methanol:ammonia(0.88) (94:6:1 v/v/v) to give the title compound as a pale yellow gum (0.033g).
Mass Spectrum: Found: MH$^+$ 494 (^{35}Cl)
Hplc System 3 (λ = 220-330nm) Rt 4.4min

Example 117
2-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2,4-difluoro-benzyl)-amino]-butyric acid trifluoroacetate
p-Benzyloxybenzylalcohol resin[10] (0.54mmol/g; 0.253g) was wetted with DMF and then treated with a mixture of 2-(9H-fluoren-9-ylmethoxycarbonylamino)-butyric acid (0.221g) and diisopropylcarbodiimide (0.107ml) in dry DMF (1ml). The mixture was agitated for 26h and then filtered dry under suction. The resin was repeatedly washed with DMF (x3), dichloromethane (x3), and diethyl ether (x3) before drying under suction. The resin was then agitated with a 20% v/v solution of piperidine in DMF (2ml) for 1.3h. After filtration the resin was repeatedly washed with DMF (x3) and dichloromethane (x3). Trimethylorthoformate (0.3ml), 2,4-difluorobenzaldehyde (0.3ml), and dichloromethane (0.9ml) were added and the mixture agitated for 4 days. The resin was filtered dry and washed with dichloromethane (x3) then a solution of tetramethylammonium triacetoxyborohydride (0.14g) and glacial acetic acid (0.03ml) in dichloromethane (1ml) was added. The resin was agitated for 2 days, filtered dry, washed with dichloromethane (x3) and DMF (x3) and a solution of 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.106g), diisopropylcarbodiimide (0.046ml), and 4-(N,N-dimethylamino)pyridine (trace) in DMF (0.75ml) was added. After agitating for 19h excess reagents were removed by filtration and the resin was washed with DMF (x3) and dichloromethane (x3) before treatment with dichloromethane (0.5ml) and 95:5 v/v trifluoroacetic acid and water (2ml). After 2h the resin was filtered and washed thoroughly with dichloromethane. The combined filtrate and washings were evaporated to dryness under reduced

pressure and subjected to preparative hplc. Evaporation of the required fraction gave the title compound as a pale cream foam (0.021g).
Hplc system 1 (λ= 254nm) Rt 8.4min
Mass spectrum: Found: MH^+ 504.1485 $C_{25}H_{24}{}^{35}ClF_2N_3O_4$ requires 504.1502

Example 118
4-[([3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-methyl]-benzoic acid trifluoroacetate

p-Benzyloxybenzylalcohol resin[10] (0.54 mmol/g; 0.25g) was wetted with DMF and then treated with a solution of 4-(chloromethyl)benzoic acid (0.23g) and diisopropylcarbodiimide (0.106ml) in DMF (1ml). The mixture was agitated overnight and the resin filtered and washed with DMF (x2) before repeating the entire coupling procedure. The resin was washed with DMF (x6) and then treated with isobutylamine (0.2ml) in DMF (0.5ml) together with a trace of sodium iodide. After agitating for 3 days the resin was filtered and washed with DMF (x3) and the amine reaction repeated this time overnight. The resin was then filtered dry, washed with DMF (x6), dichloromethane (x6) and diethyl ether (x2) and dried by suction. After wetting the resin with DMF it was treated with 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.053g), diisopropylcarbodiimide (0.021ml), and 4-(N,N-dimethylamino)pyridine (trace) in DMF (0.5ml). After agitating for 24h the resin was filtered and washed with DMF (x6) and the coupling procedure repeated. The resin was then filtered and washed with DMF (x6), dichloromethane (x6) and diethyl ether (x2) before drying by suction. The resin was treated with a 1:1 v/v mixture of trifluoroacetic acid and dichloromethane (2ml) with agitation for 80min. The resin was filtered and washed with more of the trifluoroacetic acid mixture and then dichloromethane. The combined filtrate and washings were evaporated to dryness under reduced pressue and subjected to preparative hplc. The title compound was obtained as a colourless gum (0.019g)
Hplc system 3 (λ = 220-330nm) Rt 4.2 min
Mass spectrum: Found: MH^+ 482.1864 $C_{26}H_{29}{}^{35}ClN_3O_4$ requires 482.1847

Example 119
4-[2-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-ethyl]-benzoic acid trifluoroacetate

p-Benzyloxybenzylalcohol resin[10] (0.54 mmol/g; 0.25g) was wetted with DMF and then treated with a solution of 4-(2-chloroethyl)benzoic acid (0.25g), diisopropylcarbodiimide (0.106ml) and 4-(N,N-dimethylamino)pyridine (trace) in DMF (1ml). The mixture was agitated overnight and the resin filtered and washed with DMF (x2) before repeating the entire coupling procedure. The resin was filtered and washed with DMF (x6) and then treated with isobutylamine (1ml), DMF (0.7ml) and sodium iodide (0.1g) and the resin shaken and subjected to sonication alternately for 35min. The resin was then agitated for 3 days and then filtered and washed with DMF (x6), dichloromethane (x6) and diethyl ether (x2) before drying by suction. After wetting the resin with DMF it was treated with 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.053g), diisopropylcarbodiimide (0.021ml), and 4-(N,N-dimethylamino)pyridine (trace) in DMF (0.5ml). After agitating for 24h the resin was filtered and washed with DMF (x6) and the coupling procedure repeated. The resin was then filtered and washed with DMF (x6), dichloromethane (x6) and diethyl ether (x2) before drying by suction. The resin was then treated with a 1:1 v/v mixture of trifluoroacetic acid and dichloromethane (2ml) with agitation for 1.25h. The resin was filtered and washed with more of the trifluoroacetic acid mixture and then dichloromethane. The combined filtrate and washings were evaporated to dryness under reduced pressure and subjected to preparative hplc and the title compound was obtained as a clear brown-tinged oil (0.012g).
Hplc system 1 (λ = 254nm) Rt 8.5min
Mass spectrum: Found: MH^+ 496.1990 $C_{27}H_{31}{}^{35}ClN_3O_4$ requires 496.2003

Example 120
6-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-benzyl)-amino]-hexanoic acid trifluoroacetate

p-Benzyloxybenzylalcohol resin[10] (0.54mmol/g, 0.250g) was wetted with DMF (ca. 2ml) and then treated with a mixture of 6-bromohexanoic acid (0.173g), diisopropylcarbodiimide (0.139ml) and 4-(N,N-dimethylaminopyridine (0.02g) in dry DMF (1ml). The mixture was agitated for 5 days and then filtered dry under suction. The resin was repeatedly washed with DMF (x3), and dichloromethane (x3) before drying under suction. The resin was then agitated with 2-fluorobenzylamine (1.5ml) in dry DMF (1.5ml) for 2 days. After filtration, the resin was repeatedly washed with DMF (x3) and dichloromethane (x3). The resin was then agitated with 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.16g),

diisopropylcarbodiimide (0.127ml) and 4-dimethylaminopyridine (0.012g) for 3 days. After the excess reagents were removed by filtration, the resin was washed with DMF (x3) and dichloromethane (x3) before treatment with dichloromethane (1ml) and trifluoroacetic acid (1ml). After 1.5h, the resin was filtered and washed thoroughly with dichloromethane. The combined filtrate and washings were evaporated to dryness under reduced pressure and subjected to preparative hplc. Evaporation of the required fraction gave the title compound as a gum (0.0082g).
Hplc system 1 (λ = 254nm) Rt 8.0min
Mass spectrum: Found: MH^+ 514 (^{35}Cl)

Similarly prepared, using commercially available amines, were:-

Example 121
6-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(3-fluoro-benzyl)-amino]-hexanoic acid trifluoroacetate
Hplc system 1 (λ = 254nm) Rt 8.0min; Mass spectrum: Found: MH^+ 514 (^{35}Cl)

Example 122
6-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-methoxy-ethyl)-amino]-hexanoic acid trifluoroacetate
Hplc system 1 (λ= 254nm) Rt 5.9min Mass spectrum: Found: MH^+ 464 (^{35}Cl)

Example 123
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-pyridin-4-ylmethyl-amino)-hexanoic acid trifluoroacetate
Hplc system 1 (λ= 254nm) Rt 4.4min Mass spectrum: Found: MH^+ 496 (^{35}Cl)

Example 124
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclohexylmethyl-amino)-hexanoic acid trifluoroacetate
Hplc system 1 (λ= 254nm) Rt 8.9min Mass spectrum: Found: MH^+ 502 (^{35}Cl)

Example 125
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-hexanoic acid trifluoroacetate
Hplc system 1 (λ= 254nm) Rt 7.5min Mass spectrum: Found: MH^+ 462 (^{35}Cl)

Example 126
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]benzoyl}-thiophen-2-ylmethyl-amino)-hexanoic acid trifluoroacetate
Hplc system 3 (λ= 220-330nm) Rt 3.75min Mass spectrum: Found: MH^+ 501 (^{35}Cl)

Example 127
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]benzoyl}-(2-methyl-butyl)-amino]-hexanoic acid trifluoroacetate
Hplc system 3 (λ= 220-330 nm) Rt 3.8min Mass spectrum: Found: MH^+ 476 (^{35}Cl)

Example 128
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclobutyl-amino)-butyric acid trifluoroacetate .
p-Benzyloxybenzylalcohol resin[10] (0.54mmol/g, 0.250g) was wetted with DMF (*ca.* 2ml) and then treated with a mixture of 4-bromobutanoic acid (0.112g), diisopropylcarbodiimide (0.139ml) and 4-(N,N-dimethylaminopyridine) (0.02g) in dry DMF (1ml). The mixture was agitated for 2 days and then filtered dry under suction. The resin was repeatedly washed with DMF (x3), and dichloromethane (x3) before drying under suction. The resin was then agitated with cyclobutylamine (1.5ml) in dry DMF (1.5ml) for 1 day. After filtration, the resin was repeatedly washed with DMF (x3) and dichloromethane (x3). The resin was then agitated with 3-[2-(tert-butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.16g), diisopropylcarbodiimide (0.127ml) and 4-(N,N-dimethylaminopyridine) (0.012g) for 3 days. After the excess reagents were removed by filtration, the resin was washed with DMF (x3) and dichloromethane (x3) before treatment with dichloromethane (1ml) and trifluoroacetic acid (1ml). After 1.5h, the resin was filtered and washed thoroughly with dichloromethane. The combined filtrate and washings were evaporated to dryness under reduced pressure and subjected to preparative hplc. Evaporation of the required fraction gave the title compound as a gum (0.0152g).
Hplc system 1 (λ= 254nm) Rt 6.6min
Mass spectrum: Found: MH^+ 432 (^{35}Cl)

Similarly prepared, using commercially available amines, were:

Example 129
4-[[3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl)-(3-fluoro-benzyl)-amino]-butyric acid trifluoroacetate
Hplc system 1 (λ= 254nm) Rt 7.6min; Mass spectrum: Found: MH^+ 486 (^{35}Cl)

Example 130
4-{[3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl)-furan-2-ylmethyl-amino)-butyric acid trifluoroacetate
Hplc system 1 (λ= 254nm) Rt 6.7min; Mass spectrum: Found: MH^+ 458 (^{35}Cl)

Example 131
4-[[3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl)-(1-methyl-1H-benzoimidazol-2-yl)-amino]-butyric acid trifluoroacetate
Hplc system 3 (λ = 220-330 nm) Rt 3.8min; Mass spectrum: Found: MH^+ 508 (^{35}Cl)

Example 132
4-[[3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl)-naphthalen-1-ylmethyl-amino)-butyric acid trifluoroacetate
Hplc system 3 (λ= 220-330 nm) Rt 4.2min Mass spectrum: Found: MH^+ 518 (^{35}Cl)

Example 133
N-(5-Carbamoyl-pentyl)-3-chloro-N-(2-fluoro-benzyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate
Rink amide resin[11] (0.45mmol/g, 0.250g) was treated with piperidine (20% in DMF) and agitated for 30min and then filtered dry under suction. The resin was repeatedly washed with DMF (x3) and dichloromethane (x3) before drying under suction. The resin was then treated with a mixture of 6-bromohexanoic acid (0.11g), diisopropylcarbodiimide (0.11ml) and 4-(N,N-dimethylaminopyridine) (0.02g) in dry DMF (2ml). The mixture was agitated for 24h and then filtered dry under suction. The resin was repeatedly washed with DMF (x3), and dichloromethane (x3) before drying under suction. The resin was then agitated with 2-fluorobenzylamine (1.5ml) in dry DMF (1.5ml) for 3 days. After filtration, the resin was repeatedly washed with DMF (x3) and dichloromethane (x3). The resin was then agitated with 3-[2-(tert-

butoxycarbonyl-pyridin-4-yl-amino)-ethoxy]-5-chloro-benzoic acid (0.16g), diisopropylcarbodiimide (0.127ml) and 4-(N,N-dimethylaminopyridine) (0.012g) for 3 days. After the excess reagents were removed by filtration, the resin was washed with DMF (x3) and dichloromethane (x3) before treatment with dichloromethane (2ml) and trifluoroacetic acid (0.2ml). After 1.5h, the resin was filtered and washed thoroughly with dichloromethane. The combined filtrate and washings were evaporated to dryness under reduced pressure. The residue was dissolved in a mixture of dichloromethane (2ml) and trifluoroacetic acid (1ml) and stirred at room temperature for 2h, after which the solution was evaporated to dryness under reduced pressure and subjected to preparative hplc. Evaporation of the required fraction gave the title compound as a gum (0.024g)
Hplc system 1 (λ= 254nm) Rt 7.35min
Mass spectrum: Found: MH^+ 513 (^{35}Cl)

Similarly prepared, using commercially available amines, were:

Example 134
N-(5-Carbamoyl-pentyl)-3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2,2,2-trifluoro-ethyl)-benzamide trifluoroacetate
Hplc system 1 (λ= 254nm) Rt 6.9min; Mass spectrum: Found: MH^+ 487 (^{35}Cl)

Example 135
N-(5-Carbamoyl-pentyl)-3-chloro-N-(2-methoxy-ethyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate
Hplc system 1 (λ= 254nm) Rt 5.4min; Mass spectrum: Found: MH^+ 463 (^{35}Cl)

Example 136
N-(5-Carbamoyl-pentyl)-3-chloro-N-cyclohexylmethyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate
Hplc system 3 (λ= 220-330nm) Rt 4.1min; Mass spectrum: Found: MH^+ 501 (^{35}Cl)

Example 137
N-(5-Carbamoyl-pentyl)-3-chloro-N-isobutyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 3 (λ=220-330nm) Rt 3.8min; Mass spectrum: Found: MH^+ 461 (^{35}Cl)

Example 138

N-(5-Carbamoyl-pentyl)-3-chloro-N-furan-2-ylmethyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

Hplc system 1 (λ= 254nm) Rt 6.4min; Mass spectrum: Found: MH^+ 485 (^{35}Cl)

Example 139

N-(5-Carbamoyl-pentyl)-3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-N-thiophen-2-ylmethyl-benzamide trifluoroacetate

Hplc system 3 (λ=220-330nm) Rt 3.9min; Mass spectrum: Found: MH^+ 501 (^{35}Cl)

Example 140

6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isopropyl-amino)-hexanoic acid trifluoroacetate

Hplc system 1 (λ= 254nm) Rt 7.0min; Mass spectrum: Found: MH^+ 448 (^{35}Cl)

Example 141

3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[2-(pyridin-2-yloxy)-ethyl]-benzamide)

A solution of {2-[3-chloro-5-(isopropyl-2-(pyridin-2-yloxy)-ethyl-carbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.033g) and TFA (0.4ml) in dichloromethane (0.4ml) was stirred at room temp. for 3h then concentrated under vacuum. The residue was purified by flash chromatography on silica eluting with dichloromethane/methanol/ammonia (94:6:1) to give the title compound as a colourless gum (0.005g).

Mass spectrum: Found: MH^+ 455 (^{35}Cl)

Hplc system 3 (λ = 220-330nm) Rt 3.8min

Example 142

3-Chloro-N,N-diisopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide trifluoroacetate

{2-[3-Chloro-5-(diisopropylcarbamoyl)-phenoxy]-ethyl}-pyridin-4-yl-carbamic acid tert-butyl ester (0.073g) was treated with dichloromethane (2ml) containing

trifluoroacetic acid (1ml). After 2h the excess solvents and reagents were evaporated at reduced pressure to give the title compound as a colourless gum (0.08g).

Mass spectrum: Found: MH^+ 376.1799 $C_{20}H_{27}{}^{35}ClN_3O_2$ requires 376.1791

Hplc system 1 (λ = 254nm) Rt 8.2min

References

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[4] US patent 4016267.

[5] S. Dragon *et al.*, Makromol. Chem., 1986, 187(1), 9-22.

[6] Japanese patent 60156659.

[7] J. Chem. Soc., Perkin Trans. 2. 1987, (12), 1789.

[8] US patent 5334745.

[9] Japanese patent 60156659.

[10]p-Benzyloxybenzyl alcohol resin - polymer matrix is copoly(styrene-1% divinylbenzene), 100-200 mesh; Novabiochem cat. no. 01-64-0014

[11]Rink amide resin - polymer matrix is copoly(styrene-1% divinylbenzene), 100-200 mesh; Novabiochem cat. no. 01-64-0013

Compounds of formula (I) have been included in pharmacy formulations, and details of such formulations are given below.

TABLETS FOR ORAL ADMINISTRATION

A. Direct Compression

	% w/w
Active ingredient	32.7
Anhydrous lactose	36.8
Microcrystalline cellulose	25.0
Pregelatinised maize starch	5.0
Magnesium stearate	0.5

The active ingredient was sieved and blended with the excipients. The resultant mix was compressed into tablets using a tablet machine fitted with suitable diameter punches.

A rotary machine may also be used for tabletting.

Tablets of various strengths may be prepared by for example altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

B. Wet Granulation

Formulation (i)

	% w/w
Active ingredient	3.5
Lactose	73.25
Starch	15.0
Pregelatinised maize starch	7.5
Magnesium stearate	0.75

The active ingredient was sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water were added and the powders were granulated. After drying, the granules were screened and blended with the magnesium stearate. The granules were then compressed into tablets using suitable diameter punches. The water used for granlation does not appear in the final product.

A rotary machine may also be used for tabletting.

Tablets of various strengths may be prepared by for example altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

Formulation (ii)

	% w/w
Active ingredient/lactose granule*	93.0
Microcrystalline cellulose	5.5
Crosscarmellose sodium	1.0
Magnesium stearate	0.5

* Active ingredient/lactose granule	% w/w
Active ingredient	50.0
Lactose	50.0
Purified water	qs +

+ The water does not appear in the final product. Typical range 100-140g per kg of blend.

The active ingredient and lactose were mixed together and granulated by the addition of purified water. The granules obtained after mixing were dried and passed through a screen, and the resulting granules were then mixed with the other tablet core excipients. The mix is compressed into tablets.

A rotary machine may also be used for tabletting.

Tablets of various strengths may be prepared by for example altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

The tablets may be film coated with suitable film-forming materials such as hydroxypropyl methylcellulose, preferably incorporating pigments in the formulation, using standard techniques. Alternatively the tablets may be sugar coated, or enteric coated.

Coating Suspension	% w/w
Hydroxypropyl methylcellulose	10.0
Opaspray	5.0
Purified water to	100.0++

or

Coating Suspension	% w/w
Opadry	10.0
Purified Water to	100.00 ++

++ The water does not appear in the final product.

COMPRESSION COATED TABLET

The active ingredient may also be formulated as a tablet core using conventional excipients such as fillers, binders, disintegrants and lubricants, and this core then compressed within an outer tablet (compression coated) using conventional excipients such as a pH-independent hydrophilic polymer, fillers, binders, disintegrants and lubricants. This outer coat may also contain active ingredient. The compression of both the core and the outer compression coat can be achieved using conventional tabletting machinery.

Such a dosage form can be designed so as to control the release of active ingredient as required.

EFFERVESCENT TABLET

	% w/w
Active ingredient	8.75
Sodium bicarbonate	41.03
Monosodium citrate anhydrous	41.22
Aspartame	2.5
Polyvinylpyrrolidone	2.0
Sodium benzoate	3.0
Orange flavour	1.0
Lemon flavour	0.5
Absolute alcohol for granulation	qs

The active ingredient, anhydrous monosodium citrate, sodium bicarbonate and aspartame were mixed together and granulated by the addition of a solution of the polyvinylpyrrolidone in the alcohol. The granules obtained after mixing were dried

and passed through a screen, and the resulting granules were then mixed with the sodium benzoate and flavourings. The granulated material was compressed into tablets using suitable diameter punches.

A rotary machine may also be used for tabletting.

LIQUID-FILLED CAPSULE FORMULATIONS FOR ORAL ADMINISTRATION

Liquid formulations were prepared by slow addition of active ingredient into the other ingredients with constant mixing.

Example	A % w/w	B % w/w
Active ingredient	18.2	18.2
Oleic acid	60.985	68.485
Polyethylene glycol 600	7.3	7.3
Propylene glycol	6.0	6.0
Polysorbate 80	7.5	-
Ascorbyl palmitate	0.015	0.015

The liquid formulations were filled into gelatin capsules, the size of the capsule being used and the filler determining the possible fill weight/volume and hence the dose of active ingredient per capsule.

POWDER-FILLED CAPSULES

	% w/w
Active ingredient	24.5
Lactose	75.0
Magnesium stearate	0.5

The active ingredient was sieved and blended with the excipients. The mix was filled into hard gelatin capsules using suitable machinery. The dose is determined by the fill weight and the capsule size.

SYRUP

	mg/5ml dose
Active ingredient	49.0
Hydroxypropyl methylcellulose (viscosity type 4000)	22.5
Buffer	qs
Flavour	qs
Colour	qs
Preservative	qs
Sweetener	qs
Purified water to	5.0ml

The hydroxypropyl methylcellulose was dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution was adjusted to volume and mixed. The syrup was clarified by filtration.

SUSPENSION

	mg/5ml dose
Active ingredient	49.0
Aluminium monostearate	75.0
Sweetening agent	qs
Flavour	qs
Colour	qs
Fractionated coconut oil to	5.0ml

The aluminium monostearate was dispersed in about 90% of the fractionated coconut oil. The resulting suspension was heated to 115°C while stirring and then cooled. The sweetening agent, flavour and colour were added and the active ingredient was suitably dispersed. The suspension was made up to volume with the remaining fractionated coconut oil and mixed.

SUB-LINGUAL TABLET

	% w/w
Active ingredient/lactose granule*	49.0
Compressible sugar	50.5
Magnesium stearate	0.5

The active ingredient was sieved through a suitable sieve, blended with the excipients and compressed using suitable punches. Tablets of various strengths may be prepared by altering either the ratio of active ingredient to excipients or the compression weight and using punches to suit.

A rotary machine may also be used for tabletting.

SUPPOSITORY FOR RECTAL ADMINISTRATION

Active ingredient	49.0mg
*Witepsol W32	1.0g

* A proprietary grade of Adeps Solidus Ph Eur

A suspension of the active ingredient in molten Witepsol was prepared and filled using suitable machinery, into 1g size suppository moulds.

FOR INJECTION

	% w/v
Active ingredient	1.0
Water for injections B.P. to	100

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability and/or to facilitate soution of the active ingredient using dilute acid or alkali or by the addition of suitable buffer salts. Antioxidants and metal chelating salts may also be included. The solution is clarified, made up to final volume with water and the pH re-measured and adjusted if necessary.

The solution may be packaged for injection, for example by filling and sealing in ampoules, vials or syringes. The ampoules, vials or syringes mat be aseptically filled (e.g. the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions) and/or terminally sterilised (e.g. by heating in an autoclave using one of the acceptable cycles). The solution may be packed under an inert atmosphere of nitrogen.

Preferably the solution is filled into ampoules, sealed by fusion of the glass and terminally sterilised.

FOR INHALATION

Inhalation Cartridges

	mg/cartridge
Active ingredient (micronised)	0.56
Lactose	25.00

The active ingredient was micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend was filled into No 3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges were administered using a powder inhaler such as the Glaxo Rotahaler.

Metered Dose Pressurised Aerosol

Suspension Aerosol	mg/metered dose	Per can
Active ingredient (micronised)	0.280	73.92mg
Oleic acid	0.020	5.28mg
Isopentane	23.64	5.67g
Tetrafluroethane	61.25	14.70g

The active ingredient was micronised in a fluid energy mill to a fine particle size range. The oleic acid was mixed with the above at a temperature of 10-15°C and the micronised drug was mixed into the solution with a high shear mixer. The

suspension was metered into aluminium aerosol cans and suitable metering valves, delivering 85mg of suspension, were crimped onto the cans and the dichlorodifluoromethane was pressure filled into the cans through the valves.

NASAL SPRAY

	% w/v
Active ingredient	7.0
Sodium chloride	0.9
Purified water to	100
Shot weight	100mg (equivalent to 7mg active ingredient)

The active ingredient and sodium chloride were dissolved in a portion of the water, the solution made to volume with the water and the solution thoroughly mixed.

The pH may be adjusted to facilitate solution of the active ingredient, using acid or alkali and/or subsequently adjusted if necessary taking into account the pH for optimum stability. Alternatively, suitable buffer salts may be used. The solution may be preserved with, for example, benzalkanium chloride and phenylethyl alcohol, for a multi-dose nasal spray.

Biological Results

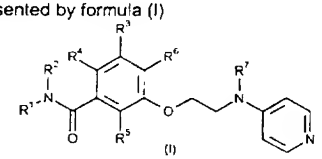
The compounds of the present invention are thrombin inhibitors. The results below illustrate the thrombin activity of a range of of compounds of formula (I) using the previously described biological method:

Example no.	IC_{50} nm
1	8
6	5
9	7
13	15
17	14
20	9
29	62
37	17
40	9

41	28
47	61
49	38
55	50
58	107
69	63
87	22
89	15
91	34
96	40
132	10
134	140
138	28
142	41
152	91

CLAIMS

1. A compound represented by formula (I)



(I)

where

R^1 and R^2 independently represent a group

or R^1 and R^2 together form a C_{3-7} heterocycloalkyl or heterocycloalkenyl group which may be optionally substituted by C_{1-6} alkyl, C_{1-4} alkoxy, halogen, carboxylic acid or a C_{1-4} carboxylic acid ester group;

R^3 represents hydrogen, C_{1-3} alkyl, halogen, or C_{1-2} alkoxy;

R^4, R^5 and R^6 independently represent hydrogen, or halogen;

R^7 represents hydrogen or C_{1-6} alkyl;

R^8 represents hydrogen, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkenyl, aryl, or heteroaryl, which groups are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyloxy, NR^9R^{10}, $NHCOR^{11}$, $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17};

X represents a bond, a C_{1-6} alkyl chain, or a C_{3-6} alkenyl chain, where one or two nitrogen, oxygen, or sulfur atoms may be optionally contained within each chain, and the chains are optionally substituted by one or more groups selected from halogen, hydroxy, CN, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}acyloxy, NR^9R^{10}, $NHCOR^{11}$ $NHSO_2R^{12}$, COR^{13}, CO_2R^{14}, $CONR^{15}R^{16}$, and SO_2NHR^{17};

R^9-R^{17} represent hydrogen, C_{1-6} alkyl, or R^9 and R^{10} or R^{15} and R^{16} form a C_{3-7} heterocycloalkyl ring, or R^{12} additionally may represent trifluoromethyl;

and pharmaceutically acceptable derivatives or solvates thereof.

2. A compound according to Claim 1 where R^1 represents a group

where X represents a bond or C_{1-6} alkyl group and R^8 represents hydrogen, C_{3-7} cycloalkyl, aryl, or heteroaryl.

3. A compound according to Claim 2 where X represents a bond and R^8 represents phenyl optionally substuituted by one or more halogen groups, or C_{3-7} cycloalkyl.

4. A compound according to Claim 2 or Claim 3 where X represents a C_{1-6} alkyl group and R^8 represents hydrogen, cycloalkyl, or heteroaryl.

5. A compound according to Claim 1 where R^2 represents a group

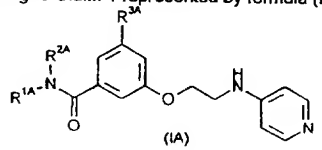
and X represents C_{3-6} alkenyl, or a C_{1-6} alkyl which optionally contains an oxgen group within the chain and is optionally substituted by a group selected from hydroxy, C_{1-6} alkoxy, $NHSO2R^{12}$, CO_2R^{14}, $CONR^{15}R^{16}$, C_{1-6} acyloxy or SO_2NHR^{17} , and R^8 represents hydrogen, C_{3-7} heterocycloalkyl, aryl optionally substituted by CO_2R^{14}, or heteroaryl optionally substituted by hydroxy or C_{1-6} alkyl.

6. A compound according to Claim 1 where R^3 represents C_{1-3} alkyl or halogen.

7. A compound according to Claim 1 where R^4 , R^5 and R^6 represent hydrogen or halogen.

8. A compound according to Claim 1 where R^7 is preferably hydrogen.

9. A compound according to Claim 1 represented by formula (IA)



(IA)

where

R^{1A} represents a group

X^A represents a bond, C_{1-6} alkyl;

R^{8A} represents hydrogen, C_{3-7} cycloalkyl, aryl optionally substituted by halogen, or heteroaryl;

R^{2A} represents a group

where

X^B represents C_{1-6} alkyl optionally substituted by CO_2R^{14A};

R^{8B} represents hydrogen, phenyl substituted by CO_2R^{14A}, oxadiazole substituted by a hydroxy group, or an unsubstituted C-linked tetrazole group;

R^{3A} represents C_{1-3} alkyl, or halogen;

and pharmaceutically acceptable derivatives or solvates thereof.

10. N-Cyclohexyl-3,N-dimethyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-cyclohexyl-N-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Bromo-N-cyclohexyl-N-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-Allyl-3-chloro-N-cyclohexyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-Allyl-3-bromo-N-cyclohexyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclohexyl-amino)-acetic acid;
({3-Bromo-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclohexyl-amino)-acetic acid;
N-Allyl-3-chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-Allyl-3-bromo-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(tetrahydro-pyran-4-yl)-benzamide;
3-Bromo-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(tetrahydro-pyran-4-yl)-benzamide;
3-Chloro-N-propyl-N-pyridin-3-yl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Bromo-N-propyl-N-pyridin-3-yl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-(3,5-difluorophenyl)-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Bromo-N-(3,5-difluorophenyl)-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
2-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2,4-difluoro-benzyl)-amino]-

butyric acid;
4-[({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-methyl]-benzoic acid;
4-[2-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-ethyl]-benzoic acid;
3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-trifluoromethanesulfonylamino-propyl)-benzamide;
3-Chloro-N-isopropyl-N-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-[2-(3-Amino-[1,2,4]oxadiazol-5-yl)-ethyl]-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-Carbamoyl-ethyl)-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

N-(2-Carbamoyl-ethyl)-3-chloro-N-cyclopropylmethyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(tetrahydro-furan-2-ylmethyl)-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-(2,2-dimethyl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-isobutyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
6-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-benzyl)-amino]-hexanoic acid;
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-hexanoic acid;
6-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-methoxy-ethyl)-amino]-hexanoic acid;
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclohexylmethyl-amino)-hexanoic acid;
6-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(3-fluoro-benzyl)-amino]-hexanoic acid;
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-pyridin-4-ylmethyl-amino)-hexanoic acid;
N-(5-Carbamoyl-pentyl)-3-chloro-N-furan-2-ylmethyl-5-[2-(pyridin-4-ylamino)-

ethoxy]-benzamide;
N-(5-Carbamoyl-pentyl)-3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2,2,2-trifluoro-ethyl)-benzamide;
N-(5-Carbamoyl-pentyl)-3-chloro-N-(2-fluoro-benzyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(5-Carbamoyl-pentyl)-3-chloro-N-(2-methoxy-ethyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(5-Carbamoyl-pentyl)-3-chloro-N-cyclohexylmethyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(5-Carbamoyl-pentyl)-3-chloro-N-isobutyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(5-Carbamoyl-pentyl)-3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-N-thiophen-2-ylmethyl-benzamide;
1-{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-piperidine-2-carboxylic acid;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclobutyl-amino)-butyric acid;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-furan-2-ylmethyl-amino)-butyric acid;
4-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(3-fluoro-benzyl)-amino]-butyric acid;
{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-(2-methyl-piperidin-1-yl)-methanone;
3-Chloro-N-(2-diethylcarbamoyl-ethyl)-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-(3-methanesulfonylamino-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-[3-(propane-1-sulfonylamino)-propyl]-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-(3-oxo-3-piperidin-1-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-[2-(ethyl-methyl-carbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-(3-oxo-3-pyrrolidin-1-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-(3-morpholin-4-yl-3-oxo-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide mixture with 3-({3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-

benzoyl}-isopropyl-amino)-propionic acid (1:2);
N-(2-tert-Butylcarbamoyl-ethyl)-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide
3-Chloro-N-[2-(2,2-dimethyl-propylcarbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-(3-oxo-3-thiomorpholin-4-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-(3-oxo-3-thiazolidin-3-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-(3-ethanesulfonylamino-propyl)-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-[3-(propane-2-sulfonylamino)-propyl]-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-(4-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-[1,2,4]triazol-1-yl-propyl)-benzamide;
3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-[1,2,4]triazol-1-yl-ethyl)-benzamide;
3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(4-[1,2,4]triazol-1-yl-butyl)-benzamide;
3-Chloro-N-(4-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-tetrazol-2-yl-propyl)-benzamide;
3-Chloro-N-(3-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-tetrazol-2-yl-propyl)-benzamide;
3-Chloro-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-tetrazol-2-yl-propyl)-benzamide;
3-Chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-tetrazol-2-yl-ethyl)-benzamide;
3-Chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-[1,2,3]triazol-2-yl-ethyl)-benzamide;
3-Chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[2-(pyridin-2-yloxy)-ethyl]-benzamide;
3-Chloro-N-isopropyl-N-(2-methoxy-ethyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-thiophen-2-ylmethyl-amino)-hexanoic acid;
6-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-methyl-butyl)-amino]-

hexanoic acid;
{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-phenyl}-(2,5-dimethyl-pyrrolidin-1-yl)-methanone;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-naphthalen-1-ylmethyl-amino)-butyric acid;
4-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(1-methyl-1H-benzoimidazol-2-yl)-amino]-butyric acid;
3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-trifluoromethanesulfonylamino-propyl)-benzamide;
N-(3-Amino-propyl)-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclopentyl-amino)-acetic acid;
3-Chloro-N-cyclopentyl-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-cyclopentyl-N-(3-hydroxy-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(tetrahydro-pyran-4-yl)-benzamide;
3-Chloro-N-cyclopentyl-N-(2,3-dihydroxy-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-cyclopentyl-N-(3-morpholin-4-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclopentyl-amino)-butyric acid ethyl ester;
3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-pyrrolidin-1-yl-propyl)-benzamide;
N-(3-Carbamoyl-propyl)-3-chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-Carbamoylmethyl-3-chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-ethyl-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-cyclopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N,N-dipropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclopentyl-amino)-butyric acid;
N-(2-Carbamoyl-ethyl)-3-chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-(2-chloro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
4-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-phenyl)-amino]-butyric acid methyl ester;
4-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-phenyl)-amino]-butyric acid;
3-Chloro-N-(2-fluoro-phenyl)-N-(4-oxo-4-pyrrolidin-1-yl-butyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(3-Carbamoyl-propyl)-3-chloro-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
4-((2-Carbamoyl-phenyl)-{3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-amino)-butyric acid methyl ester;
4-((2-Carbamoyl-phenyl)-{3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-amino)-butyric acid;
3-Chloro-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[3-(1H-tetrazol-5-yl)-propyl]-benzamide;
3-Chloro-N-[2-(2,3-dihydroxy-propoxy)-ethyl]-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
(*R*)-1-{3-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-phenyl)-amino]-propyl}-pyrrolidine-2-carboxylic acid;
3-Chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-sulfamoyl-ethyl)-benzamide;
3-Chloro-N-[2-(ethyl-methyl-carbamoyl)-ethyl]-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-[2-(ethyl-methyl-carbamoyl)-ethyl]-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-tert-Butylcarbamoyl-ethyl)-3-chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-[2-(2,2-dimethyl-propylcarbamoyl)-ethyl]-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

3-Chloro-N-(3-oxo-3-thiomorpholin-4-yl-propyl)-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-(3-oxo-3-thiazolidin-3-yl-propyl)-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-tert-Butyl-3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-[2-(1-methyl-1H-tetrazol-5-yl)-ethyl]-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-(3,5-difluoro-phenyl)-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-(3-morpholin-4-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(tetrahydro-pyran-4-yl)-benzamide;
3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(3-pyrrolidin-1-yl-propyl)-N-(tetrahydro-pyran-4-yl)-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-(1-propyl-butyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-cyclopentyl-N-(4-oxo-4-pyrrolidin-1-yl-butyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-ethyl-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[1,3,4]thiadiazol-2-yl-benzamide;
3-Chloro-N-propyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-thiazol-2-yl-benzamide;
3-Chloro-N-[2-(2,3-dihydroxy-propoxy)-ethyl]-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-tert-Butylsulfamoyl-ethyl)-3-chloro-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-(2-isopropylsulfamoyl-ethyl)-N-phenyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[2-(pyridin-2-yloxy)-ethyl]-benzamide;
3-Chloro-N-[2-(2,3-dihydroxy-propoxy)-ethyl]-N-(4-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[2-(1H-tetrazol-5-yl)-ethyl]-benzamide;

3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-[1,2,4]triazol-1-yl-ethyl)-benzamide;

3-Chloro-N-[2-(3-methyl-but-2-yl-carbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide,
3-Chloro-N-[2-(3,3-dimethyl-but-2-yl-carbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide,
3-Chloro-N-[2-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-tert-Butyl-N-(2-tert-butylcarbamoyl-ethyl)-3-chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-tert-Butylcarbamoyl-ethyl)-3-chloro-N-cyclobutyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-cyclobutyl-N-[2-(2,2-dimethyl-propylcarbamoyl)-ethyl]-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(2-Carbamoyl-ethyl)-3-chloro-N-cyclobutyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide ;
3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-(2-sulfamoyl-ethyl)-benzamide ;
3-Chloro-N-(2,2-dimethyl-propylsulfamoyl-ethyl)-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide ;
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isopropyl-amino)-hexanoic acid ;
N-(2-tert-Butylcarbamoyl-ethyl)-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
N-(5-tert-Butylcarbamoyl-pentyl)-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide ;
3-Chloro-N-[5-(2,2-dimethyl-propylcarbamoyl)-pentyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide ;
N-(5-Carbamoyl-pentyl)-N-isopropyl-3-methyl-5-[2-pyridin-4-ylamino)-ethoxy]-benzamide ;
3-Chloro-N-(2-(4-tert-butylphenyl)-ethyl)-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)ethoxy]-N-[3-(2,2-dimethyl-propionylamino)-propyl]-benzamide;
3-Chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)ethoxy]-N-[3-(3,3-dimethyl-butyrylamino)-propyl]-benzamide;
3-Chloro-N-[2-(1,1-dimethyl-propylcarbamoyl)-ethyl]-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

N-{2-(2,2-dimethylpropylcarbamoyl)-ethyl}-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-(Isopropyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-amino)-propionic acid;
3-(Isopropyl-{3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-amino)-propionic acid methyl ester;
N-(5-tert-Butylcarbamoyl-pentyl)-3-chloro-N-isopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
6-({3-Methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isopropyl-amino)-hexanoic acid;
N-(2-Cyano-ethyl)-N-isopropyl-3-methyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N,N-diisopropyl-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;
3-Chloro-N-isopropyl-N-(3-oxo-3-thiazolidin-3-yl-propyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-benzamide;

and pharmaceutically acceptable derivatives or solvates thereof.

11. 3-Chloro-N{2-(5-hydroxy-[1,2,4]oxadiazol-3-yl)-ethyl}-N-isopropyl-5-[2[(pyridin-4-ylamino)-ethoxy]-benzamide ;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclobutyl-amino)-butyric acid;
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-hexanoic acid;
4-[({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-methyl]-benzoic acid ,
4-[2-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-isobutyl-amino)-ethyl]-benzoic acid;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclopentyl-amino)-butyric acid ethyl ester;
4-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclopentyl-amino)-butyric acid;
3-Chloro-N-cyclopentyl-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[2-(1H-tetrazol-5-yl)-ethyl]-benzamide;
6-({3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-cyclohexylmethyl-amino)-hexanoic acid;

6-{{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]benzoyl}-thiophen-2-ylmethyl-amino}-hexanoic acid;

4-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-phenyl)-amino]-butyric acid methyl ester;

4-[{3-Chloro-5-[2-(pyridin-4-ylamino)-ethoxy]-benzoyl}-(2-fluoro-phenyl)-amino]-butyric acid;

3-Chloro-N-(2-fluoro-phenyl)-5-[2-(pyridin-4-ylamino)-ethoxy]-N-[3-(1H-tetrazol-5-yl)-propyl]-benzamide;

and pharmaceutically acceptable derivatives or solvates thereof.

12. A compound according to any one of Claims 1 to 11 for use in therapy.

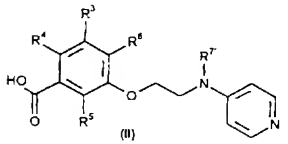
13. A method of treatment of a mammal, including man, suffering from a condition susceptible of amelioration by a thrombin inhibitor comprising administration of an effective amount of a compound according to any one of claims 1 to 11 or a pharmaceutically acceptable derivative thereof.

14. The use of a compound according to any one of claims 1 to 11 or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment of a condition susceptible of amelioration by a thrombin inhibitor.

15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 11 or a pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers.

16. A process for preparing a compound of formula (I) as claimed in Claim 1, or a pharmaceutically acceptable derivative thereof which comprises:

(A), reaction of a compound of formula (II) with a compound of formula (III),

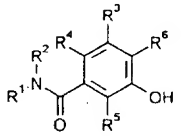


(II)

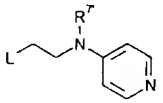
(III)

where $R^{7'}$ represents R^7 or a suitable protecting group such as tert-butoxycarbonyl,

(B), reaction of compounds of formula (XIV) and (XV)



(XIV)



(XV)

where L is a suitable leaving group, in the presence of a suitable base, or

(C), reaction of compounds of formula (II) with compounds of formula (III) which are bound to a solid phase resin via a carboxamide or carboxylate functional group on R^3 or X, by amide coupling techniques, followed by deprotection of any protecting groups and cleavage from the resin under suitable conditions.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/EP 96/05743

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/74 A61K31/44 C07D405/12 C07D413/12 A61K31/535
C07D401/12 C07D417/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	CHEM REV., 1996, pages 3170-3171,3176, XP002027890 PATANI ET AL: "A rational approach in drug design" References on page 2171 show that the general concept of the citations (listed on page 3176) was known well before the priority date. ---	1-16
X	WO 94 20467 A (BOEHRINGER MANNHEIM GMBH) 15 September 1994 cited in the application see claim 1 ---	1-16
P,A	US 5 556 977 A (WAYNE) 17 September 1996 see claim 1 -----	1-12

[ ] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 1997	18.04.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Gettins, M

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PCT/EP 96/05743

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09/08/2004, EAST Version: 1.4.1